CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205122Orig1s000

CHEMISTRY REVIEW(S)

To: Memo-to-File

From: Charles Jewell, Ph.D. - CMC reviewer for NDA 205122 and Olen Stephens, Ph.D - CMC Branch 1 Branch Chief

Subject: NDA 205122 (Topiramate Extended Release Capsules)- Recommendation For Approval From a CMC Perspective

Date: 15-Jan-2014

Our initial review (filed 07-Jan-2014) indicated a recommendation for approval pending the finalization of the decision from Biopharmaceutics with respect to the suitability of the biopharmaceutical data presented in NDA 205122 as amended with response to directed information requests. This decision is finalized and filed by Biopharmaceutics reviewers Sandra Suarez Sharp, Ph.D./ Angelica Dorantes, Ph.D on 15-Jan-2014.

Based on their approval recommendation, the overall recommendation from the chemistry, manufacturing and controls perspective is approval. No additional comments need to be communicated to the applicant.

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

/s/

CHARLES F JEWELL
01/16/2014

OLEN M STEPHENS
01/16/2014

NDA 205122

Topiramate Extended Release Capsules

Upsher Smith Laboratories Inc.

Charles F. Jewell Jr.
Division of Neurology Products

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 205122

2. REVIEW #1

3. REVIEW DATE: 07-Jan-2013

4. REVIEWER: Charles F. Jewell Jr.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND-069257 - Topiramate (b) (4) and amendments	05-MAR-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 205122 SDN 1 New NDA	11-FEB-2013
NDA 205122 SDN 2 Multiple Amendments, includes biopharmaceutics; reviewed by ONDQA Biopharmaceutics Reviewer (Sandra Suarez)	21-MAY-2013
NDA 205122 SDN 6 Quality Response to IR; this is biopharmaceutics information reviewed by ONDQA Biopharmaceutics Reviewer (Sandra Suarez)	30-AUG-2013
NDA 205122 SDN 7 Labeling/Package Insert Draft	19-SEP-2013
NDA 205122 SDN 9 Quality Response to IR; contains CMC and Biopharmaceutics Info	28-OCT-2013
NDA 205122 SDN 11 Labeling/Package Insert Draft and multiple categories	02-DEC-2013

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Upsher Smith Laboratories
Address:	6701 Evenstad Drive Maple Grove, Minnesota 55369
Representative:	
Telephone:	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Qudexy XR
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anticonvulsants (2010300)

11. DOSAGE FORM: Capsule, Extended Release

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

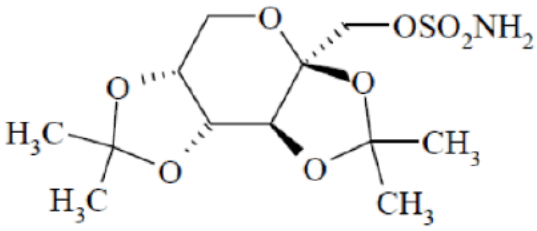
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Chemistry Review Data Sheet

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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



Topiramate

Molecular Formula: $C_{12}H_{21}NO_8S$
Molecular Weight: 339.36

IUPAC: 2,3;4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate
Other Chemical Names:

- 2,3;4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate
- β-D-Fructopyranose, 2,3;4,5-bis-*O*-(1-methylethylidene)-sulfamate

Company Code:

- (b) (4)
- Upsher-Smith Laboratories, Inc.: Topiramate, USP (USL255)

Chemical Abstracts: 97240-79-4

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	N/A		LOA: 26-Oct-2012
	IV			4	N/A		LOA: 26-Oct-2012
	III			4	N/A		LOA: 31-Oct-2012
	III			4	N/A		LOA: 1-Nov-2012

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		LOA: 23-Jul-2012
	III			4	N/A		LOA: 13-Aug-2012
	II			3	Adequate	19-Nov-2013	LOA: 18-Oct-2012: Reviewer Qiuxia Wang for ANDA 091185
	III			4	N/A		LOA: 26-Oct-2012
	IV			4	N/A		LOA: 12-Dec-2012
	IV			4	N/A		LOA: 13-Dec-2012

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			Ohidul I. Siddiqui
EES	Overall acceptable	22-JUL-2013	C. Capacci-Daniel
Pharm/Tox			J. Edward Fisher
Biopharm			Sandra Suarez
Clinical Pharmacology			Joo Yeon Lee Ta-Chen Wu
Methods Validation	Not Required		
Medication Errors			Liu, Liu
EA	Adequate	06-DEC-2013	Charles Jewell
Microbiology	Not Required		

The Chemistry Review for NDA 205122

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An approval is still pending adequate responses regarding the acceptance of dissolution specification criteria by ONDQA biopharmaceutics. There are no other quality deficiencies pending. The Office of Compliance has rendered an acceptable recommendation for the manufacturing and testing facilities (22-Jul-13).

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

II. Summary of Chemistry Assessments

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

This drug product is topiramate in an extended release formulation, in capsules. It is developed as a treatment for initial monotherapy and adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures and adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome. The capsules are designed to be used for once daily dosing. The applicant is substantially relying on the Agency's findings of safety and effectiveness for Topamax® (topiramate) Tablets, NDA 020505, by Janssen Pharmaceuticals, Inc., for approval of this application for USL255 Topiramate Extended-Release (ER) Capsules, submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(b)(2)).

The capsules are manufactured in five strengths, each capsule has a grey body with a unique colored cap (25 mg, light pink cap, capsule size 4; 50 mg golden yellow cap, capsule size 3; 100 mg, reddish brown cap, capsule size 1; 150 mg, pale yellow cap, capsule size 0 and 200 mg, brown cap, capsule size 0el). "Upsher-Smith" is printed on the cap in black ink for all strengths, accept the 200 mg strength which uses white printing. For each strength, the amount of topiramate in milligrams and the letters mg are printed in black ink on the body. Each strength is packaged in bottles with counts of 30, 90 and 500 capsules (b) (4) Each bottle is white HDPE with (b) (4) caps and foil induction seals, (b) (4)

The formulation for the beads used to fill the capsules is the same for all capsules. (b) (4)

[redacted] The formulation of the coated beads is the same for the proposed commercial formulation (designated formulation MK) as was used in pivotal clinical studies (designated formulation MJ). The difference between the trials product and the commercial product is color for all strengths and the size of the capsule used for the 200 mg strength; formulation MJ uses size 00 and formulation MK uses size 0el. [redacted] The formulation uses microcrystalline cellulose [redacted] hypromellose [redacted] ethylcellulose [redacted] hypromellose [redacted] diethyl phthalate [redacted] Capsule components are hypromellose, titanium dioxide, [redacted] and various amounts of black iron oxide, red iron oxide and yellow iron oxide depending on color. In all cases, excipients do not exceed the precedent according to the inactive ingredients database maintained by the Agency. The drug product is intended for use when dosed as whole capsules or when capsules are opened and sprinkled on food.

The drug substance is known by its USAN name, topiramate. The IUPAC name is 2,3,4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate. Its aqueous solubility varies with pH with 5.1 mg/mL at pH=1.0 to 21.0 mg/mL at pH 9.8. Its solubility at pH=7.4 is 11.5 mg/mL. It exists as a [redacted] and is manufactured and supplied by [redacted] Type II Drug Master File (DMF) No. [redacted]). It is manufactured [redacted] It is a white solid with a [redacted] There is a USP monograph for topiramate and impurity levels comply with the monograph specification limits. The USP defined impurities are [redacted] Fructose and topiramate related impurity A [redacted].

The drug substance is controlled in the specification by description, identification by IR, identification by HPLC, water content, residue on ignition, specific rotation, assay (HPLC), heavy metals, impurities (related compound A, any specified, and total by HPLC), fructose (HPLC), sulfate/sulfamate (Ion Chromatography), residual solvents [redacted] and particle size [redacted]. These criteria were determined with adequate support from batch history and compliance with the USP monograph. The USP monograph does not specify particle size distribution. [redacted] A retest period of [redacted] is established for this drug substance.

The process development for the drug product manufacturing process was described in detail in the application. Several formulation campaigns were run during development, to produce the formulation used in the pivotal studies. The proposed commercial formulation is the same, except for the coloring in the capsule shells, and the size of the capsule for the 200 mg strength. The manufacturing process [redacted]

[redacted] (b) (4) There are two manufacturing sites for this drug product (USL Denver and [redacted] (b) (4)). There are equipment capacity differences between the two sites, there is adequate data to verify the equivalence of product from both sites. [redacted] (b) (4) The release and stability specifications are identical for both sites. Registration stability data is provided for all sites, but long term stability is used to assign expiration dating based on 24 months of testing on material from the pivotal clinical trials and commercial formulation material manufactured at the USL Denver site. Data for some of the commercial material is only completed for 12 to 21 months, with commitment to complete these studies. The Agency agreed to assign expiration dating based on long term stability studies on the current registration data, at a pre-NDA meeting. Based on this data, 24 months expiration dating is assigned to all strengths and all configurations.

Deficiencies currently remain before approval can be recommended. See the basis for approvability below for a listing of required information.

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

The capsules were developed as a treatment for initial monotherapy and adjunctive therapy for patients with partial onset or primary generalized tonic-clonic seizures and adjunctive therapy for patients with seizures associated with Lennox-Gastaut syndrome. The extended release capsules were developed for once daily dosing.

C. Basis for Approvability or Not-Approval Recommendation

An approval is still pending, requiring adequate responses to the following:

- Acceptance of dissolution specification criteria by ONDQA biopharmaceutics.

III. Administrative

A. Reviewer's Signature
B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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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.

/s/

CHARLES F JEWELL
01/07/2014

OLEN M STEPHENS
01/07/2014
CMC recommendation is pending biopharmaceutics evaluation of dissolution method and specifications.

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

OND Division:	Division of Neurology Products
NDA:	205122
Applicant:	Upsher-Smith Laboratories
Stamp Date:	11-Feb-2013
PDUFA Date:	11-Dec-2013
Trademark:	(b) (4) is proposed
Established Name:	Topiramate
Dosage Form:	Extended release capsule
Route of Administration:	Oral
Indication:	Antiepileptic
CMC Lead:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☐	☒

Summary and Critical Issues:

Summary

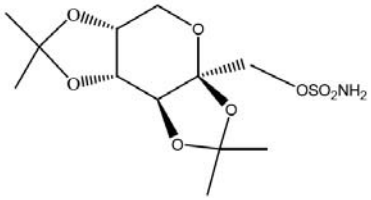
Topiramate was originally developed by Ortho McNeil/Janssen Pharmaceuticals (Ortho) for treatment of epilepsy. The innovator product, Topamax® (topiramate) Tablets was approved under NDA 20-505 in 1996. Currently Ortho markets Topamax® Tablets 25 mg, 50 mg, 100 mg, and 200 mg for treatment of epilepsy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

Upsher-Smith Laboratories (USL) has developed an extended release (XR) capsule formulation of topiramate. In this 505(b)(2) NDA, the firm proposes marketing topiramate XR capsules for: monotherapy in patients 10 years of age and older with partial onset seizures or primary generalized tonic-clonic seizures; adjunctive therapy adults and pediatric patients (2 to 16 years of age) with partial onset seizures or primary generalized tonic-clonic seizures; and adjunctive therapy in patients 10 years of age and older with seizures associated with Lennox Gastaut syndrome. The firm is not seeking an indication for migraine prophylaxis.

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 $C_{12}H_{21}NO_8S$ and molecular weight 339.4.

The chemical structure of topiramate is:



The bulk drug substance is manufactured by (b) (4) under DMF (b) (4) which is cross-referenced for CMC information. The DMF was reviewed previously, and found adequate (Qiuxia Wang, 05-Apr-2012). The DMF however, has been updated since the last review.

Limited manufacturing 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 USL specification for topiramate (applicant's Table 1) is based on the USP monograph with the addition of particle size and residual solvent testing. Non-compendial methods and corresponding methods validation reports are provided.

Table 1: Specifications for Topiramate Drug Substance

Test	Upsher-Smith Analytical Method	Proposed Acceptance Criteria
Description	TM-00001	White to off-white powder
ID A [IR]	USP TM-00040[1]	IR scan exhibits maxima similar to the reference standard.
ID B [HPLC]	USP TM-00372	The retention time (RT) of the major peak in the sample chromatogram is similar to the RT of the major peak in the standard chromatogram. RT difference is NMT (b) (4) minutes.
Water Content [Karl Fischer]	USP TM-00030	NMT 0.5%
Residue on Ignition	USP	NMT 0.2%
Specific Rotation	USP	Between –28.6° and –35.0°
Assay [HPLC]	USP TM-00372	98.0 – 102.0%, on anhydrous basis
Heavy Metals	USP (Method II)	NMT (b) (4) (NMT 10 ppm)
Impurities [HPLC]	USP TM-00372	Related Compound A: NMT 0.3% Any Unspecified: NMT 0.10%[2] Total: NMT 0.5%
Fructose [HPLC]	USP TM-00181	NMT 0.3%
Sulfate/ Sulfamate (b) (4)	USP TM-00174	Sulfate: NMT (b) (4) ppm[3] Sulfamate: NMT (b) (4) ppm[3]
Residual Solvents (b) (4)	USP TM-00043	(b) (4) NMT (b) (4) ppm[4] (b) (4) NMT (b) (4) ppm[5] (b) (4) NMT (b) (4) ppm[6]
Particle Size	TM-00175	(b) (4)

1. IR Identification differs from USP Infrared Absorption <197> method; USL does not use KBr.
2. USP acceptance criteria is 0.1%. USL specification reflects current ICH reporting requirement to two significant figures versus USP acceptance criteria of 0.1%.
3. USP acceptance criteria is NMT 0.1%.
4. ICH acceptance criteria is (b) (4) ppm. USL has adopted the ICH specification; reference is made to 3.2.S.4.5 for justification of specification.
5. ICH acceptance criteria is (b) (4) ppm. USL has tightened the acceptance criteria; reference is made to 3.2.S.4.5 for justification of specification.
6. ICH acceptance criteria is (b) (4) ppm. USL has tightened the acceptance criteria; reference is made to 3.2.S.4.5 for justification of specification.

It is noted that the applicant proposes relatively wide acceptance criteria for particle size distribution. Given the high solubility of topiramate it is unlikely that particle size would impact on drug release. The impact, if any, of particle size on manufacturability should be assessed during the review.

Drug Product

The proposed dosage form is an extended release capsule containing 25 mg, 50 mg, 100 mg, 150 mg, or 200 mg of topiramate intended for once daily dosing. The capsule fill, which is a common formulation for all strengths, consists of topiramate, microcrystalline cellulose and hypromellose beads. (b) (4) The composition of 200 mg Topiramate Extended-Release Capsules is given in applicant's Table 1.

Table 1: Topiramate Extended-Release (ER) Capsules 200 mg (USL255-200-MK)

Ingredient	Function	Base Formulation (% w/w)[1]	mg/capsule[1]	Overall Formulation (% w/w)[1]	IIG Maximum (solid oral) mg/dose
Core Bead Components					
Topiramate, USP	Drug substance	(b) (4)			(b) (4)
Microcrystalline Cellulose, NF (b) (4)					
Hypromellose 2910, USP (b) (4)					
(b) (4)					
Coating Components					
Ethylcellulose, NF (b) (4)					(b) (4)
Hypromellose 2910, USP (b) (4					
					(b) (4)
Hypromellose 2910, USP					(b) (4)
Titanium Dioxide, USP (b) (4					
Black Iron Oxide, NF[5]					
Red Iron Oxide, NF[5]					
Yellow Iron Oxide, NF[5]					
		Theoretical Total	**598**	**100.0**	

[1] Values are rounded to nearest 0.00%, 1 mg or 0.0%, respectively.

(b) (4)

The pharmaceutical development section incorporates some QbD elements. Development of the capsule formulation itself appears to have been somewhat empirical and included nine formulations used for clinical (BA/BE) studies. The applicant does describe of DOEs around critical material attributes, e.g., hypromellose and ethylcellulose viscosity. The applicant used DOEs more extensively for development and optimization of the proposed commercial manufacturing process.

Topiramate extended release capsules will be manufactured by USL at the firm's Denver, CO facility and by a contract manufacturer, (b) (4) (b) (4) The manufacturing process involves All unit operations are commonly used in manufacture of solid oral dosage forms, including extended-release capsules. However, the manufacturing process description in the NDA is not very detailed, and master batch records were not provided. Additional information will be requested.

The drug product specification is outlined in applicant's Table 1.

Table 1: Specification

Test	Test Method	Acceptance criteria
Description	TM-00001	**Release and Stability Specification:** Capsules with χ cap and grey body containing white to tan beads with "Upsher–Smith" printed on the cap in ω ink and "α mg" printed on the body in black ink. Where: USL255-25-MK: χ = light pink, α = 25, ω = black USL255-50-MK: χ = golden yellow, α = 50, ω = black USL255-100-MK: χ = reddish brown, α= 100, ω = black USL255-150-MK: χ = pale yellow, α = 150, ω = black USL255-200-MK: χ = brown, α = 200, ω = white
Identification (HPLC)	TM-00470	**Release Specification:** The retention time (RT) of the major peak in the sample chromatogram is similar to the RT of the major peak in the standard chromatogram. RT difference is NMT (b) (4) min.
Identification (IR)	TM-00415[1] TM-00040	**Release Specification:** IR scan exhibits maxima similar to that of the reference standard.
Uniformity of Dosage Units, Weight Variation	USP	**Release Specification:** (L_1) n = 10 units, AV NMT (b) (4) (L_2) n = 30 units, AV NMT (b) (4) Each unit NLT (b) (4) M and Each unit NMT (b) (4) M (b) (4) The value of M is a reference value dependent on the average % L.C.
Assay	TM-00470	**Release and Stability Specification:** (b) (4)
Degradation Products	TM-00470	**Release and Stability Specification:** (b) (4) A. Each Specified Identified (b) (4) NMT (b) (4) B. Any Unspecified: NMT (b) (4) C. Total: NMT (b) (4)
(b) (4)	TM-00176	**Release Specification:** A. (b) (4) NMT (b) (4) ppm

Test	Test Method	Acceptance criteria
		B. (b) (4) NMT (b) (4) ppm **Stability Specification:** A. (b) (4) NMT (b) (4) ppm B. (b) (4) NMT (b) (4) ppm
Dissolution	TM-00370	**Release and Stability Specification:** L_1: 1 hour: each unit NMT (b) (4) 2 hours: each unit (b) (4) 6 hours: each unit NLT (b) (4) L_2: Reference Current USP L_3: Reference Current USP
(b) (4)		

[1] TM-00415 refers to the general IR procedure TM-00040 for operation of the spectrometer.

The proposed test parameters are appropriate for an extended-release product and consistent with the existing USP for immediate-release topiramate tablets. The proposed analytical procedures include reverse-phase HPLC with refractive index detector, for assay, related substances and identification, ion chromatography for inorganic impurities (b) (4) The methods appear relatively straight-forward and adequately described to permit substantive review. It is noted that the applicant designates "release" and "stability" specifications. The firm should be reminded that the regulatory specification should include all test parameters.

Topiramate extended release capsules will be marketed in HDPE bottles with (b) (4) (b) (4) closures, and desiccant packets, or canisters based on bottle size and fill. (b) (4) fill sizes, i.e., 30-count, (b) (4) 90-count, and 500-count, are proposed. (b) (4)

With regard to product stability, a 24 month expiration dating period is proposed. The applicant present batches of two different product formulations, designated as USL255-α-MJ (Phase 3 clinical formulation) and USL255-α-MK (commercial formulation), where α represents capsule strength, as primary stability batches. The differences between formulations include changes to capsule color by varying amounts of iron oxides, differences in bottle sizes, and, for the 200 mg capsule, a change in capsule size from 00 to 0el. Data are available for product manufactured at both proposed commercial sites. The available primary data includes:

USL255-α-MJ (USL): 24 months long-term data/6 months accelerated data
25 mg. 50 mg, 100 mg, and 200 mg capsules
30-count and 90-count bottles with (b) (4) closure
500-count bottles with (b) (4) closure

USL255-α-MK (USL): 21 months data
25 mg. 50 mg, 100 mg, and 200 mg capsules
30-count and 90-count bottles with (b) (4) closure
500-count bottles with (b) (4) closure

USL255-α-MK [redacted]: 12 months data/6 months accelerated data
25 mg200 mg capsules
30-count bottles with [redacted] closure
500-count bottles with [redacted] closure

The applicant indicates that for stability studies commercial scale bead batches were split and encapsulation into multiple strengths. Although this practice is not unusual for registration studies, each combination of bead batch, encapsulation batch and bottle size (or open dish) has been assigned a unique batch number. The batch details tables provided in P.8.1 list the packaged batch number, with no encapsulation or bead batch information. Thus, it is difficult to determine how many coated bead batches were manufactured for stability studies.

The post approval commitment provides for completion of ongoing studies and placement of the *first* production scale batch of the 25 mg and 200 mg product strength at each site packaged in each packaging configuration on long-term stability. Thereafter, the applicant proposes placement of at least one lot of the lowest and highest strengths in each packaging size/ configuration manufactured that year on stability, and placement of the bracketed strengths (50 mg, 100 mg, and 150 mg) on stability over a three cycle. The applicant's justification for this approach is that *"Significant accelerated and controlled room temperature data are provided in this application for* [redacted] *commercial scale batches;.."*. The bracketing approach for post approval commitment batches is reasonable, subject to review; as is the proposal to rotate annual batches for the intermediate strengths. The applicant's characterization of the registration batches as [redacted] commercial scale batches is incorrect. The applicant will be asked to revise the post approval commitment.

Critical issues for review

Drug Substance:

No critical issues can be identified based on information provided in the NDA. As noted above, the impact of particle size on product quality should be assessed.

Drug Product:

The applicant provides detailed information regarding product and manufacturing process development. The description of the manufacturing process itself, however, is relatively less detailed and no master batch records are provided. Submission of more detailed process descriptions or master batch records should be requested.

The adequacy of the registration stability data to support the proposed shelf life is dependent on the number of unique coated bead batches used to manufacture the finished capsule batches. Given the presentation of stability information in the NDA this can not be easily determined. It is recommended that the applicant be asked to compile this information. It is also noted that the encapsulation batch sizes were generally much lower than [redacted] The acceptability of this should be determined by the reviewer.

Acceptability of the USL255-α-MJ capsule batches as primary stability batches should be determined by the reviewer.

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 manufacturing facilities identified in the application were entered into EES on 14-Mar-2013.

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 capsules) and the labeled potency.

Comments for 74-Day Letter

No 74-Day comments were identified. The following comments may be considered by the reviewer for inclusion in the 'mid-cycle' information request.

1) With regard to manufacture of the product, you indicate in Module 3.2.P.3.3 that encapsulation batch size is variable depending on the bead batch size and commercial batch size need. Revise the batch formula and manufacturing process description to include discrete batch sizes for encapsulation (b) (4).

2) In accordance with CFR 314.50 d(1)(ii)(c) a complete description of the commercial scale drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section P.3.3 of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

3) With regard to the drug product specification, in Module 3.2.P.5.1 you designate acceptance criteria for Identification (HPLC and IR), Uniformity of Dosage Units, and (b) (4) as release specifications. It is understood that the intent is to differentiate tests that are normally only performed at product release from stability indicating tests. Confirm that the products, if tested, will conform to all listed tests and acceptance criteria throughout shelf life.

4) Given the presentation of stability batch information in Modules 3.2.8.1 and 3.2.P.8.3, it is unclear which encapsulation and packaging (b) (4) were derived from each coated bead batch. Provide summary information that correlates each coated bead batch to the resultant stability batches. We recommend that this information be provided in a tabular format such as shown below.

USL255-α-MJ Stability Batch Summary

Coated Bead Batch Number	Capsule Strength	Encapsulation Batch Number (Batch Size)	Bottle Fill	Packaged Batch Number	Data Available (Months)	Storage condition
X0001	25 mg	00001 (b) (4)	30-count	12345	24 12 6	25 °C/60% RH 30 °C/65% RH 40 °C/75% RH
			90-count	12346		
			90-count	12347		
	50 mg	00002 (b) (4)	30-count	12348	24 12 6	25 °C/60% RH 30 °C/65% RH 40 °C/75% RH
			90-count	12349		
			90-count	12350		
	100 mg	00003 (b) (4)	30-count	12351	24 12 6	25 °C/60% RH 30 °C/65% RH 40 °C/75% RH
			90-count	12352		
			90-count	12353		

5) The post approval stability commitment provided in Module 3.2.P.8.2 is not acceptable. As registration stability batches of the different strengths were manufactured by encapsulating and packaging (b) (4) of the coated bead batches, we do not consider them to be commercial scale batches. Therefore, revise the protocol to provide for long-term and accelerated stability data for capsule batches manufactured and packaged at full commercial scale. The post approval commitment should include a sufficient number of batches from each manufacturing site to allow for confirmation of the tentative expiration dating period assigned during NDA review.

Review, Comments and Recommendation:

The NDA is considered fileable from a CMC perspective.

The drug substance is not a new molecular entity and the drug product design (i.e., bead in capsule) is not novel. The product is an extended-release formulation and the sponsor requests a biowaiver for the lower strengths. 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

Ramesh Sood, Ph.D.
Branch Chief

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Numbers: 205122 **Applicant: Upsher Smith Laboratories** **Stamp Date: 11-Feb-2013**

Drug Name: Topiramate extended release capsules **NDA Type: Standard**

FILING REVIEW CHECKLIST

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?	--	--	N/A for electronic submission
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	--	--	N/A

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 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 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		

* 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 ASSESSMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion request per 21 CFR § 25.31 (a).

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	X		By cross-reference to DMF (b) (4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	X		By cross-reference to DMF (b) (4)
15.	Does the section contain information on impurities?	X		Information provided in NDA and by cross-reference to DMF (b) (4)
16.	Does the section contain information regarding the characterization of the DS?	X		By cross-reference to DMF (b) (4)
17.	Does the section contain controls for the DS?	X		Information provided in NDA and by cross-reference to DMF (b) (4)
18.	Has stability data and analysis been provided for the drug substance?	X		By cross-reference to DMF (b) (4)
19.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
21.	Does the section contain container and closure information?	X		By cross-reference to DMF (b) (4)

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	X		
23.	Does the section contain information on composition?	X		
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
25.	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		
26.	Is there a batch production record and a proposed master batch record?		X	Master batch record is not provided.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	No clinical investigations other than BE were performed in support of this application.
28.	Have any biowaivers been requested?	X		Requested for lower strengths
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
30.	Does the section contain controls of the final drug product?	X		
31.	Has stability data and analysis been provided to support the requested expiration date?	X		
32.	Does the application contain Quality by Design (QbD) information regarding the DP?			Information regarding DOEs performed during development is provided. No other QbD information.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	X		

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?			N/A

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	X		
37.	Have the immediate container and carton labels been provided?	X		
38.	Does section contain trade name and established name?	X		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

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

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

/s/

MARTHA R HEIMANN
05/24/2013

RAMESH K SOOD
05/24/2013