CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206030Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: APPROVE

NDA206030
Review # 3

Drug Name/Dosage Form	Injection
Strength	200 mg/20 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Lundbeck LLC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission/Class 2	*21-Apr-2016*	*Drug Product, Facilities*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Andrei Ponta	Branch 1/DNDP 1/ONDP
Process	N/A	
Microbiology	N/A	
Facility	Viviana Matta/Ruth Moore	Branch 1/DIA/OPF
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heiman	Branch 1/DNDP 1/ONDP
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

From Review No. 1, Dr. Shastri Bhamidipati, 23-Aug-2014

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Carbamazepine	1	Adequate	Aug-19-2014	
	III		(b) (4)	3	Adequate		Last reviewed Donald Klein, Sep-25-2012
	III			3	Adequate		Last reviewed for the referenced item Jan-25-2012
	III			3	Adequate		
	IV			3,4	Adequate		
	V			3	Adequate		Last reviewed May-30-2014

[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: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Carbamazepine Injection

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 206030 is recommended for Approval.

II. Summary of Quality Assessments

A. Product Overview

Carbamazepine was originally developed by Ciba-Geigy (Novartis) for use as an antiepileptic drug. It was first approved in 1968 and is available in several oral dosage forms. However, due to poor aqueous solubility, no parenteral products have been approved. The applicant has developed a sterile, aqueous solution for intravenous administration in which carbamazepine is solubilized as a betadex sulfobutyl ether sodium (SBECD) complex. When the product is administered, the carbamazepine-SBECD complex dissociates rapidly to release carbamazepine.

The proposed product, CARNEXIV, is a sterile, aqueous solution containing 200 mg carbamazepine per 20 mL (10 mg/mL). The product also contains (b) (4) mg SBECD per 20 mL, and sodium phosphate monobasic dihydrate (b) (4) CARNEXIV is supplied in a single dose, type I glass vial with (b) (4) rubber stopper and flip off seal. The product is for intravenous use only and must be diluted in a compatible diluent (i.e., 0.9% sodium chloride, lactated ringers, or 5% dextrose prior to infusion) prior to administration.

Proposed Indication	Use as a replacement therapy for oral carbamazepine formulations, when oral administration is temporarily not feasible, in adults with partial seizures with complex symptomatology, generalized tonic-clonic seizures, or mixed seizure patterns.
Duration of Treatment	Not more than seven days
Recommended Daily Dose	70% of the prescribed oral dose administered in 4 divided doses
Maximum Daily Dose	1120 mg
Alternative Methods of Administration	None appropriate for the intended patient population

B. Quality Assessment Overview

The Agency received the original submission of NDA 206030 on December 23, 2013. Shastri Bhamidipati reviewed all Quality information except Microbiology, which was reviewed by Stephen Langille. At the end of the first review cycle, there were no outstanding Microbiology issues, and all manufacturing facilities associated with the manufacturing, testing and packaging Carbamazepine Injection were deemed acceptable. However, Dr. Bhamidipati recommended a Complete Response (CR) due to outstanding deficiencies. In the October 23, 2014, CR letter, the Agency cited three CMC issues, which are repeated below.

> *"You have not provided the requested critical extractables data from storage of the drug product admixtures in diluent bags. You need to provide the extractable data from the drug product admixtures in diluent bags with a safety evaluation of the exposure levels to the extractable components.*
>
> *"Your proposed acceptance limit of no more than* (b) (4) *mOsm/kg for osmolality of the drug product at release and shelf-life is not acceptable considering: a) the statement that osmolality of the drug product is around* (b) (4) *mOsm/kg (Section 3.2.P.2.3 of Pharmaceutical development) and b) you have not provided osmolality data for any of the drug product batches except for commercial scale development batch #921921. We recommend that you set the acceptance limit for the osmolality of the drug product based on observed levels of the drug product osmolality and provide sufficient data that scientifically justify the acceptance limit for osmolality of the drug product.*
>
> *"Additionally, we acknowledge that you intend to submit the root-cause investigation report for commercial scale development batch #921921 when you respond to the application deficiencies."*
>
> Note: The final CR comment refers to the observation of visible particles in one commercial scale development batch. The applicant's root-cause investigation for this out of specification result was not complete at the time of the original action.

The applicant resubmitted the NDA on April 8, 2016. The firm's responses to the deficiencies cited in the CR letter were evaluated by Andrei Ponta and found acceptable. [Refer to Drug Product Assessment.]

The acceptability of facilities associated with the manufacturing, testing and packaging of CARNEXIV was reevaluated by Viviana Matta. All facilities are recommended for approval and an overall Approve recommendation was entered in Panorama on June 2, 2016. [Refer to Facility Assessment.]

C. Special Product Quality Labeling Recommendations (NDA only)

There are no special labeling recommendations.

D. Final Risk Assessment (See Attachment)

Application Technical Lead Signature:

Martha R. Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
Date: 2016.08.29 14:39:53 -04'00'

Martha R. Heimann, Ph.D.
CMC Lead – Neurology
Office of New Drug Products

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Chemistry Review Data Sheet

NDA 206030

Carbamazepine Injection
10 mg/mL

Lundbeck, LLC

Division of Neurology Products, HFD 120

Shastri Bhamidipati, PhD
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date: 23-Dec-2013
PDUFA Goal Date: 23-Oct-2014

Shastri P. Bhamidipati -S

Digitally signed by Shastri P. Bhamidipati -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396781, cn=Shastri P. Bhamidipati -S
Date: 2014.10.10 10:47:31 -04'00'

Chemistry Review Data Sheet

Olen Stephens -A

Digitally signed by Olen Stephens -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -A, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.10.10 13:13:22 -04'00'

Chemistry Review Data Sheet

1. NDA 206030

2. REVIEW #: 2

3. REVIEW DATE: 10-OCT-2014

4. REVIEWER: Shastri Bhamidipati, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 206030 SD# 16	09-Sep-2014
NDA 206030 SD# 18	29-Sep-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Lundeck, LLC

Address: 4 Parkway North
Deerfield, IL 60015 USA

Representative: Wendy Tian,
Director, US Regulatory Affairs
4 Parkway North
Deerfield, IL 60015 USA

Telephone: 847-282-5761

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Carbella
b) Non-Proprietary Name (USAN): Carbamazepine Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Neurology, Antiepilectic replacement therapy

11. DOSAGE FORM: Injection, Solution

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: ___X___ Rx ___OTC

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

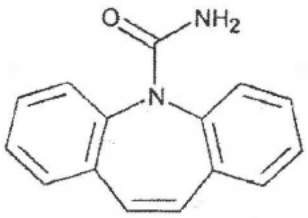
___X___Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Name(s):

1. Chemical Name: 5H-Dibenz[b_2f]azepine-5-carboxamide



Synonym
CAS-No: [298-46-4]
Molecular Formula: $C_{15}H_{12}N_2O$
Molecular Mass: 236.27

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Carbamazepine	1	Adequate	Aug-19-2014	Shastri Bhamidipati
	III		(b) (4)	3	Adequate		Last reviewed Donald Klein, Sep-25-2012
	III			3	Adequate		Last reviewed for the referenced item Jan-25-2012
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Carbamazepine Injection

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	N/A		
EES	Acceptable	17-Feb-2014	J. Williams
Pharm/Tox			
Biopharmaceutics	Not applicable		
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Tradename Carbella Acceptable	05-Feb-2014	Zerislassie, Ermias
EA	Acceptable		
Microbiology	Recommended Approval	26-Aug-2014	Stephen Langille, PhD.

Chemistry Review for NDA 206030

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 206030 for Carbamazepine Injection (10 mg/mL) cannot be approved during this review cycle due to unresolved drug product quality issues that pose potential safety issues to patients from CMC perspective. This review comprises of an evaluation of applicant's responses to CMC issues communicated on Aug-26-2014. The Office of Compliance has provided an overall recommendation for all the manufacturing sites. For comprehensive overview, please refer to the primary quality review (dated Aug-23-2014) filed in DARRTS for this NDA. A list of deficiencies is presented at the end of this review.

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

None applicable.

II. Summary of Quality Assessments

A. Drug Product [Carbamazepine Injection, 10 mg/mL] Quality

In this NDA, Lundbeck proposes marketing of a sterile, aqueous solution containing 200 mg/20 mL Carbamazepine and (b) (4) mg/20 mL betadex sulfobutyl ether sodium (solubilizing agent) for intravenous administration. The Applicant is seeking approval of NDA for a 200 mg/20 mL carbamazepine injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referencing NDA 16608 (Tegretol® 200 mg IR tablets) and NDA 20234 (Tegretol® 400 mg XR tablets) both marketed by Novartis. The proposed indication is for short term replacement of oral Carbamazepine in seizure patients when oral therapy is not feasible. The recommended dose is 70% of the prescribed oral dose administered in 4 divided doses. The applicant is relying on open label pharmacokinetic and safety studies to support approval of the NDA. The drug product is a sterile, aqueous, solution containing 10 mg/mL of Carbamazepine, betadex sulfobutyl ether sodium as a solubilizing agent and sodium phosphate monobasic dihydrate (b) (4) to be administered intravenously following dilution with a suitable diluent vehicle. The drug product is packaged in a type I glass vial with (b) (4) rubber stopper and flip off seal. The product does not contain preservatives, and intended for single use only.

Pharmaceutical development studies of Carbamazepine drug product were minimally described and comprised of optimizing the SBECD content to achieve targeted carbamazepine concentration as a homogeneous solution without precipitation and growth of extraneous particles at ambient temperature. The manufacturing process is (b) (4)

(b) (4) The finished drug product has been determined to be hypertonic due to SBECD content necessitating dilution prior to administration. However, the proposed specification for the drug product did not include testing for osmolality as a critical quality attribute. The analytical methods for release and stability testing of the drug product have been adequately described and validated establishing their suitability for the intended use. Batch analysis and stability data were presented for three pilot scale registration batches and one commercial scale demonstration batch. Stability data presented for the three registration batches include 30-36 months at 5°C, 42 months at 25°C/60% RH and 6 months at 40°C/75% RH. The stability data show that there were no significant changes in any of the tested quality attributes of the drug product, in particular, carbamazepine assay and the impurities. However, samples stored at 5°C failed for visual inspection at 30 month interval. It was also noted that one of the related impurities, (b) (4) slightly on stability with maximum observed value not exceeding (b) (4)% at long term storage up to 42 months. Photostability and temperature cycling studies show no significant changes in the drug product quality attributes. Hence, the recommended storage temperature for the drug product is 20°C – 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on available stability data, proposed shelf-life of 36-months is recommended for Carbamazepine injection, 10 mg/mL, when stored at 20°C to 25°C.

B. Drug Substance [Carbamazepine] Quality Summary

Carbamazepine was originally developed by Ciba-Geigy (Novartis) for use as an antiepileptic drug and it is a well characterized small neutral molecule. The chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide), with molecular formula $C_{15}H_{12}N_2O$ and molecular weight 236.27. Carbamazepine has very limited water solubility, (b) (4) Carbamazepine is known to have at least four different polymorphic forms and these forms have been well characterized. The drug substance used in the development of the proposed new dosage form was sourced from (b) (4) whereas the drug substance for commercial manufacturing of the drug product is sourced from (b) (4) The bulk drug substance produced by (b) (4) The applicant cross-referenced (b) (4) DMF (b) (4) for supporting chemistry, manufacturing and controls information of Carbamazepine. This DMF has been reviewed and deemed adequate to support this NDA. The drug substance will be tested for microbiological aspects (Bacterial endotoxins and microbial limits) at the drug product manufacturing site. Batch analysis data for three batches sourced from the two vendors were provided. Considering the new dosage form of proposed drug product and the maximum proposed daily dose (relative oral dose), the acceptance limits for identified impurities, namely, (b) (4) to be compliant with ICH Q3B limits. Additionally, testing and acceptance limits for residual solvents have been recommended in the specification for drug substance (b) (4).

C. Product Risk Assessment based on Product Design & Process

Risk Assessment of the Drug Product at IQA Stage

Product Design FMECA – Carbamazepine Injection

Product CQAs	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (s)	Detectability (D)	RPN
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	4 – 2 = 2 [1]	5 (Others)	5	50
Endotoxin, Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive Endotoxin Levels	(b) (4)			
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents				
Uniformity of Dose (Fill Volume/deliverable volume)	Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	2	4 (HRD [3])	2	16
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Edema	2	3 (SVP)	2	12
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Embolism	3	5 (IV)	3	45
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Generation of impurities	(b) (4)			

Executive Summary Section

Risk Assessment of the Drug Product after Primary Review

Product CQAs	Changes & Variations	Failure Mode	Initial Risk Ranking	Mitigation	Final Risk Ranking
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	Medium	Drug product is (b) (4)	Medium
Endotoxin, Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive Endotoxin Levels	Medium	Bacterial endotoxin levels in API were revised per Microbiology	Medium
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents	Low	No change in evaluation	Low
Uniformity of Dose (Fill Volume/deliverable volume)	Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	Low	No change in evaluation	Low
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Edema	Low	Osmolality testing of finished product. Assurance of diluted admixture isotonicity	Low
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Embolism	Medium	Drug product is (b) (4)	Low
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Generation of impurities	Low	No change in evaluation	Low
Appearance (Color/turbidity/visible particles)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Degradation	Low	No change in evaluation	Low

[1] Product is (b) (4)
[2] Designated as moderately stable based on proposed product specification.
[3] Designated as high risk drug; carbamazepine is considered to have a narrow therapeutic index.
[4] Finished drug product is hypertonic and diluted admixtures could be hypertonic
[5] Storage of diluted admixtures could potentially enhance extractables
[6] pH not considered since buffered to pH 5 - 7

Executive Summary Section

Risk Assessment of the Drug Product after Overall Quality Review

Product CQAs	Changes & Variations	Failure Mode	Risk Mitigation	Risk Ranking
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	Drug product is (b) (4)	Low
Endotoxin, Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive Endotoxin Levels	Bacterial endotoxin levels are controlled in API	Low
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents	Drug product has been shown to be stable (through proposed shelf-life)	Low
Uniformity of Dose (Fill Volume/deliverable volume)	Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	Fill weight and deliverable volumes monitored	Low
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Edema	Osmolality testing of finished product. Assurance of diluted admixture isotonicity	Low
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Embolism	Drug product (b) (4) (b) (4)	Low
Leachable extractables*	• Formulation • Container closure • Diluent bags • Raw materials • Process parameters • Scale/equipment • Site	• Generation of impurities	Limit storage of prepared admixtures for administration	Medium*
Appearance (Color/turbidity/visible particles)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Degradation • Visible particles	100% visual inspection	Low

[1] Product is (b) (4)
[2] Designated as moderately stable based on proposed product specification.
[3] Designated as high risk drug; carbamazepine is considered to have a narrow therapeutic index.
[4] Finished drug product is hypertonic and diluted admixtures could be hypertonic
[5] Storage of diluted admixtures could potentially enhance extractables
[6] pH not considered since buffered to pH 5 - 7
*Extractables from diluent bags have not been evaluated

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

The drug product, Carbamazepine Injection (10mg/mL) supplied as 20 ml/vial is intended for intravenous administration after dilution with suitable diluent vehicle (0.9% Sodium chloride Injection, 5% Dextrose Injection and Lactated Ringer's Solution) in the range of 0.7 mg/mL to 2.2 mg/mL over 30 minutes four times a day.

E. Basis for Approvability or Not-Approval Recommendation

The NDA applicant failed to provide requested critical quality information in regards to extractables data from storage of the drug product admixtures in diluent bags for evaluation. In the absence of this information which poses potential safety concerns for intended patient population, a complete response is recommended for this application from CMC perspective.

III. Administrative

II. Summary of Quality Assessments

ONDQA/DNDQAI /Lead/M. Heimann
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/O.Stephens

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NDA 206030

Carbamazepine Injection
10 mg/mL

Lundbeck, LLC

Division of Neurology Products, HFD 120

Shastri Bhamidipati, PhD
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date: 23-Dec-2013
PDUFA Goal Date: 23-Oct-2014

Table of Contents

Chemistry Review Data Sheet

1. NDA 206030

2. REVIEW #: 1

3. REVIEW DATE: 23-AUG-2014

4. REVIEWER: Shastri Bhamidipati, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 206030 Original Submission	20-Dec-2013
NDA 206030 SD# 4	30-Jan-2014
NDA 206030 SD# 5	27-Mar-2014
NDA 206030 SD# 6	11-Apr-2014
NDA 206030 SD# 13	05-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Lundeck, LLC

Address: 4 Parkway North
Deerfield, IL 60015 USA

Chemistry Review Data Sheet

Representative: Wendy Tian,
Director, US Regulatory Affairs
4 Parkway North
Deerfield, IL 60015 USA

Telephone: 847-282-5761

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Carbella
b) Non-Proprietary Name (USAN): Carbamazepine Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(2)

10. PHARMACOL. CATEGORY: Neurology, Antiepilectic replacement therapy

11. DOSAGE FORM: Injection, Solution

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

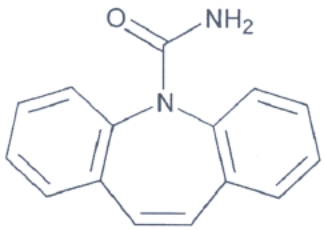
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Name(s):

1. Chemical Name: 5H-Dibenz[b_2f]azepine-5-carboxamide



Synonym
CAS-No: [298-46-4]
Molecular Formula: $C_{15}H_{12}N_2O$
Molecular Mass: 236.27

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Carbamazepine Injection

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	N/A		
EES	Acceptable	17-Feb-2014	J. Williams
Pharm/Tox	Pending		
Biopharmaceutics	Not applicable		
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Tradename Acceptable		
EA	Pending		
Microbiology	Pending		

Chemistry Review for NDA 206030

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 206030 for Carbamazepine Injection (10 mg/mL) can be approved from CMC perspective pending resolution to quality issues that were listed at the end of this review. The Office of Compliance has provided an overall recommendation for all the manufacturing sites.

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

None applicable.

II. Summary of Quality Assessments

A. Drug Product [Carbamazepine Injection, 10 mg/mL] Quality

In this NDA, Lundbeck proposes marketing of a sterile, aqueous solution containing 200 mg/20 mL Carbamazepine and (b) (4) mg/20 mL betadex sulfobutyl ether sodium (solubilizing agent) for intravenous administration. The Applicant is seeking approval of NDA for a 200 mg/20 mL carbamazepine injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referencing NDA 16608 (Tegretol® 200 mg IR tablets) and NDA 20234 (Tegretol® 400 mg XR tablets) both marketed by Novartis as the listed drugs. The proposed indication is for short term replacement of oral Carbamazepine in seizure patients when oral therapy is not feasible. The recommended dose is 70% of the prescribed oral dose administered in 4 divided doses. The applicant is relying on open label pharmacokinetic and safety studies to support approval of the NDA. The drug product is a sterile, aqueous, solution containing 10 mg/mL of Carbamazepine, betadex sulfobutyl ether sodium as a solubilizing agent and sodium phosphate monobasic dihydrate (b) (4) to be administered intravenously following dilution with a suitable diluent vehicle. The drug product is packaged in a type I glass vial with (b) (4) rubber stopper and flip off seal. The product does not contain preservatives, and intended for single use only.

Pharmaceutical development studies of Carbamazepine drug product were minimally described and comprised of optimizing the SBECD content to achieve targeted carbamazepine concentration as a homogeneous solution without precipitation and growth of extraneous particles at ambient temperature. The manufacturing process is (b) (4) The finished drug product has been determined to be hypertonic due to SBECD content necessitating dilution prior to administration. However, the proposed specification for the drug product did not include testing for osmolality as a critical

quality attribute. The analytical methods for release and stability testing of the drug product have been adequately described and validated establishing their suitability for the intended use. Batch analysis and stability data were presented for three pilot scale registration batches and one commercial scale demonstration batch. Stability data presented for the three registration batches include 30-36 months at 5°C, 42 months at 25°C/60% RH and 6 months at 40°C/75% RH. The stability data show that there were no significant changes in any of the tested quality attributes of the drug product, in particular, carbamazepine assay and the impurities. However, samples stored at 5°C failed for visual inspection at 30 month interval. It was also noted that one of the related impurities, (b) (4) slightly on stability with maximum observed value not exceeding (b) (4)% at long term storage up to 42 months. Photostability and temperature cycling studies show no significant changes in the drug product quality attributes. Hence, the recommended storage temperature for the drug product is 20°C – 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on available stability data, proposed shelf-life of 36-months is recommended for Carbamazepine injection, 10 mg/mL, when stored at 20°C to 25°C.

B. Drug Substance [Carbamazepine] Quality Summary

Carbamazepine was originally developed by Ciba-Geigy (Novartis) for use as an antiepileptic drug and it is a well characterized small neutral molecule. The chemical name is 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide), with molecular formula $C_{15}H_{12}N_2O$ and molecular weight 236.27. Carbamazepine has very limited water solubility, which is approximately 0.2 mg/mL at 25°C. Carbamazepine is known to have at least four different polymorphic forms and these forms have been well characterized. The drug substance used in the development of the proposed new dosage form was sourced from (b) (4) whereas the drug substance for commercial manufacturing of the drug product is sourced from (b) (4) The bulk drug substance produced by (b) (4) The applicant cross-referenced (b) (4) DMF (b) (4) for supporting chemistry, manufacturing and controls information of Carbamazepine. This DMF has been reviewed and deemed adequate to support this NDA. The drug substance will be tested for microbiological aspects (Bacterial endotoxins and microbial limits) at the drug product manufacturing site. Batch analysis data for three batches sourced from the two vendors were provided. Considering the new dosage form of proposed drug product and the maximum proposed daily dose (relative oral dose), the acceptance limits for identified impurities, namely, (b) (4) to be compliant with ICH Q3B limits. Additionally, testing and acceptance limits for residual solvents have been recommended in the specification for drug substance (b) (4).

C. Initial Product Risk Assessment based on Product Design & Process

Risk Assessment of the Drug Product at IQA Stage

Product Design FMECA – Carbamazepine Injection

Product CQAs	Changes & Variations	Failure Mode	Probability of Occurrence (O)	Severity of Effect (s)	Detectability (D)	RPN
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	4 – 2 = 2 [1]	5 (Others)	5	50
Endotoxin, Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive Endotoxin Levels				(b) (4)
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents				
Uniformity of Dose (Fill Volume/deliverable volume)	Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	2	4 (HRD [3])	2	16
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Edema	2	3 (SVP)	2	12
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Embolism	3	5 (IV)	3	45
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Generation of impurities				(b) (4)

Risk Assessment of the Drug Product after Primary Review

Product CQAs	Changes & Variations	Failure Mode	Initial Risk Ranking	Mitigation	Final Risk Ranking
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Non-sterile unit(s)	Medium	Drug product is (b) (4)	Medium
Endotoxin, Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	• Excessive Endotoxin Levels	Medium	Bacterial endotoxin levels in API were revised per Microbiology	Medium
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Impurity formation due to excipient reactions or unspecified reactions • Hydrolytic degradation (moisture) • Organic solvents	Low	No change in evaluation	Low
Uniformity of Dose (Fill Volume/deliverable volume)	Formulation • Container closure • Process parameters • Scale/equipment • Site	• Insufficient dose	Low	No change in evaluation	Low
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Edema	Low	Osmolality testing of finished product. Assurance of diluted admixture isotonicity	Low
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Irritation • Embolism	Medium	Drug product is (b) (4)	Low
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	• Generation of impurities	Low	No change in evaluation	Low
Appearance (Color/turbidity/visible particles)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	• Degradation	Low	No change in evaluation	Low

[1] Product is (b) (4)
[2] Designated as moderately stable based on proposed product specification.
[3] Designated as high risk drug; carbamazepine is considered to have a narrow therapeutic index.
[4] Finished drug product is hypertonic and diluted admixtures could be hypertonic
[5] Storage of diluted admixtures could potentially enhance extractables
[6] pH not considered since buffered to pH 5 - 7

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

The drug product, Carbamazepine Injection (10mg/mL) supplied as 20 ml/vial is intended for intravenous administration after dilution with suitable diluent vehicle (0.9% Sodium chloride Injection, 5% Dextrose Injection and Lactated Ringer's Solution) in the range of 0.7 mg/mL to 2.2 mg/mL over 15-30 minutes four times a day.

E. Basis for Approvability or Not-Approval Recommendation

III. Administrative

II. Summary of Quality Assessments

ONDQA/DNDQAI /Lead/M. Heimann
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/

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/s/

SHASTRI P BHAMIDIPATI
08/23/2014

OLEN M STEPHENS
08/23/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206030

2. DATES AND GOALS:

Letter Date:	20-Dec-2013
Submission Received Date:	23-Dec-2013
PDUFA Goal Date:	23-Oct-2014

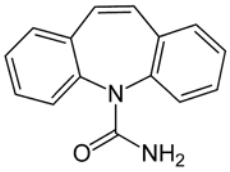
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Carbella is proposed
Established or Non-Proprietary Name (USAN):	Carbamazepine
Dosage Form:	Injection
Route of Administration	Intravenous
Strength(s)	10 mg/mL
Rx/OTC Dispensed:	Rx

4. INDICATION:

Replacement therapy in adults (18 years and older) who are on a stable maintenance oral dose of carbamazepine when oral administration is not feasible.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT: Lundbeck LLC

7. SUBMISSION PROPERTIES:

Review Priority	Standard
Submission Classification:	3
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization:	DNP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS/DATE OF REQUEST
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		Submitted 16-Jan-2014. As of 17-Feb-2014, EES indicates acceptable overall recommendation.
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	Categorical exclusion claim provided but will need revision to include "extraordinary circumstances" statement.
CDRH		X	
Other		X	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? YES

CMC Filing Issues: N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes

CMC Comments for 74-Day Letter:

1) Submit a comprehensive regulatory acceptance specification for carbamazepine (i.e., test parameters, analytical procedures, and acceptance criteria) to the NDA. 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. You may incorporate USP compendial methods by reference. Provide all other analytical procedures and supporting method validation data in the application.

2) You propose intravenous administration of 70% of the corresponding oral carbamazepine dose. As this is a new route of administration, provide justification for any drug substance impurity that exceeds the ICH Q3A qualification threshold (b) (4)

3) Provide data regarding the solubility of carbamazepine in aqueous betadex sulfobutyl ether sodium solution at reduced temperature (e.g., (b) (4)). Additionally, provide refrigeration to (b) (4)) temperature cycling results for at least one stability batch.

4) Provide data to support the physical and chemical compatibility of the product with manufacturing equipment, (b) (4).

5) Provide data to support the physical and chemical compatibility of the product with the labeled diluents, infusion bags and IV tubing.

6) Revise the process description [Module 3.2.P.3.3] to include labeling and packaging procedures. Provide master batch production records for labeling and packaging.

7) The proposed acceptance criterion of not more than (b) (4)% for (b) (4) in the drug product exceeds the ICH Q3B qualification threshold (0.2%) corresponding to a maximum daily dose equal to 1120 mg (70% of 1600 mg). Revise the limit for consistency with ICH or provide data to support the proposed limit.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? YES
Biopharmaceutics Filing Issues: N/A
Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? NO
Biopharmaceutics Comments for 74-Day Letter: N/A

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes, per Microbiology filing review (Stephen Langille, 16-Jan-2014).
Microbiology Filing Issues: N/A

Summary of Initial Quality Assessment

Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended? Yes
CMC Reviewer, Microbiology Reviewer

Summary of Critical Issues and Complexities
CMC Critical Issues and Complexities *Drug Substance*—As, discussed below, reliance on the USP Carbamazepine monograph is inadequate. The monograph does not include controls for process solvents and the applicant did not provide data to support use of the compendial impurities method to control the (b) (4) impurity. Acceptability of impurity acceptance criteria should be determined in consultation with the nonclinical reviewer. *Drug Product*—As discussed below, the drug product is a sterile, aqueous solution containing a highly water insoluble active ingredient. Thus, robustness of the formulation is a critical issue. There are also concerns with regard to chemical stability and presence of (b) (4) as a degradation product.

Biopharmaceutics Critical Issues or Complexities

Submission:
The Applicant is seeking approval of a New Drug Application (NDA) for a 200 mg/20 mL carbamazepine (CBZ) injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, referencing NDA 16608 (Tegretol® 200 mg IR tablets) and NDA 20234 (Tegretol® 400 mg XR tablets) both marketed by Novartis as the listed drugs. The proposed drug product is a parenteral antiepileptic drug formulation intended as replacement therapy in adults (18 years and older) who are on a stable maintenance oral dose of carbamazepine when oral administration is not feasible.

In support of the proposed IV formulation and the switch from treatment with oral CBZ to IV CBZ, the Applicant conducted study OV-1015: A Sequential, Open-Label Study of the Pharmacokinetics and Safety of Intravenous Carbamazepine Relative to Oral Carbamazepine in Adult Patients with Epilepsy. This study will be reviewed by the Clinical Pharmacology Reviewer. A Biowaiver request is not applicable for this NDA and is not submitted in this NDA.

Recommendation:
This NDA is fileable from the Biopharmaceutics perspective.

This NDA submission does not require further assessment from the ONDQA-Biopharmaceutics team. Therefore, this filing review concludes the Biopharmaceutics involvement for this NDA.

Initial Quality Assessment

Background

Carbamazepine (CBZ) was developed by Ciba-Geigy (now Novartis) for use as an antiepileptic drug and for treatment of trigeminal neuralgia. The initial approval was in 1968. CBZ is currently available as tablets, chewable tablets, extended-release tablets and oral suspension (Novartis), extended-release capsules (Shire/Validus), and generic equivalents.

In this 505(b)(2) NDA, Lundbeck proposes marketing of a sterile, aqueous solution containing 200 mg/20 mL CBZ and (b) (4) mg/20 mL betadex sulfobutyl ether sodium (solubilizing agent) for intravenous administration. The proposed indication is for short term replacement of oral CBZ in seizure patients when oral therapy is not feasible. The recommended dose is 70% of the prescribed oral dose administered in 4 divided doses. The applicant relies on open label pharmacokinetic and safety studies to support approval of the NDA.

Drug Substance

CBZ (chemical name: 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide), is a well characterized, neutral, small molecule with molecular formula $C_{15}H_{12}N_2O$ and molecular weight 236.27. The key physical characteristic of CBZ relative to the proposed product is its limited water solubility, which is approximately (b) (4)

The proposed drug substance manufacturer for commercial production bulk drug substance is (b) (4) The applicant cross-references (b) (4) DMF (b) (4) for supporting manufacturing and control information. The DMF appears to have been reviewed several times by OGD. The most recent reviewer (D. Green, 10-Sep-2012) found the DMF adequate, with information requests. Subsequent amendments were not reviewed.

Although (b) (4) will be the supplier for commercial production, clinical and primary registration stability drug product batches were manufactured using drug substance batches obtained from (b) (4) The applicant provides a comparison of batch analysis data for (b) (4) drug substance lots used to manufacture registration stability batches of CBZ injection versus drug substance batches manufactured by (b) (4) in Table 1, Module 3.2.S.2.6. The impurities reported for (b) (4) sourced CBZ are (b) (4) Per information in Module 3.2.P.5.5, the latter impurity is the (b) (4) . Residual solvents are (b) (4) .

With regard to specifications, the applicant references the USP monograph and states that the drug product manufacturer will also test for endotoxins and microbial limits on receipt. The applicant references the current USP for analytical procedures.

Reviewer comments

The applicant should provide supporting data to verify that the USP method can detect, and adequately control, the (b) (4) *impurity*

The USP monograph limit for related compounds is not more than 0.2% for any individual impurity. However, this exceeds the ICH Q3A identification and qualification thresholds (both (b) (4) *The acceptability of the USP acceptance criteria for a new dosage form and route of administration should be determined in consultation with the nonclinical reviewer.*

The application does not include an analytical procedure for determination of the residual solvents; and this is not part of the USP monograph. Absence of a test procedure is potentially a reason to refuse to file the NDA; however, this is a readily correctable deficiency.

The reviewer should determine, based on the significance of any changes reported subsequent to the last review, whether the manufacturer's DMF should be re-reviewed.

Drug Product

The proposed product is a sterile, aqueous, solution containing CBZ 200 mg/20 mL for intravenous infusion. The solution also contains betadex sulfobutyl ether sodium (SBECD) and sodium phosphate monobasic dihydrate. The product may contain sodium hydroxide and/or hydrochloric acid to adjust pH. The drug product is packaged in a type I glass vial with (b) (4) rubber stopper and flip off seal. The product does not contain preservatives, and is for single use only.

Carbamazepine Injection, 10 mg/mL

Name of Ingredient	Quantity per mL	Function	Reference to Standard[1]
DRUG SUBSTANCE Carbamazepine	10 mg	Active ingredient	USP
EXCIPIENTS Sodium phosphate monobasic dihydrate	(b) (4)		USP
Betadex sulfobutyl ether sodium			NF
Sodium hydroxide[2]			NF
Hydrochloric acid[2]			NF
Water for Injection			USP
			(b) (4)

[1]The current pharmacopoeia is used
[2] Added as a 1 N solution, as necessary to adjust pH.

Source: Module 3.2.P.1.

CBZ Injection will be manufactured by Baxter Pharmaceutical Solutions in Bloomington, Indiana. The manufacturing process involves (b) (4) [redacted]

The applicant provides minimal information regarding formulation development in Module 3.2.P.2.2. The applicant chose 10 mg CBZ per mL as the target concentration. Use of alcoholic solvents or co-solvents did not provide a high enough concentration. Therefore, the applicant chose to use a solubility enhancer. SBECD was chosen based on previous use in FDA-approved products. (b) (4) [redacted]

(b) (4) [redacted]

The proposed specification for CBZ Injection is shown below.

Table 1. Specification for Carbamazepine Injection, 10 mg/mL.

Test	Method	Specification
Sterility	USP General Chapter <71>, Sterility Tests	Sterile
Appearance	Visual	Pass (clear, colorless to light yellow solution)
Visual Inspection	USP General Chapter <1>, Injections	Pass (free from visible particulate)
pH	USP General Chapter <791>, pH	(b) (4)
Assay for Carbamazepine	HPLC	
Related Substances:		
(b) (4)	HPLC	
	HPLC	
	HPLC	
Other Unknown Individual Impurity	HPLC	
Total Impurities	HPLC	
Carbamazepine Identification[1]	HPLC (retention time agreement)	Positive
Carbamazepine Identification[1]	UV (absorbance ratio agreement)	Positive
Assay for Betadex sulfobutyl ether sodium (SBECD)	HPLC	(b) (4)
Particulate Matter	USP <788>, Particulate Matter	Meets USP
Bacterial Endotoxins	USP General Chapter <85>, Bacterial Endotoxins	(b) (4)
Volume in Container[1]	USP General Chapter <1>, Volume in Container	

[1]These tests are performed for batch release only.
NMT = Not More Than
NLT = Not Less Than

Source: Module 3.2.P.1.

Reviewer comments

Test parameters and acceptance criteria are typical for a sterile, parenteral product and the analytical procedures appear straightforward. . The HPLC procedure used for carbamazepine assay and impurities appears similar to the USP method for carbabmazepine. SBECD assay is determined by size exclusion. Based on product stability data, the applicant proposes an acceptance criterion of NMT (b) (4) % for (b) (4). This exceeds the ICH Q3B qualification threshold (0.2% for 1120 mg daily dose) and will require consultation with the nonclinical team.

With regard to product stability, a 36 month expiration dating period is proposed. The applicant provides data for three pilot scale ((b) (4) batches manufactured from (b) (4) -sourced drug substance. These batches are designated as primary stability and were stored at 5°C (30 to 36 months), 25°C/60% R. H. (42 months) and 40°C/75% R. H. (6 months). The applicant also provides supportive data for two clinical batches and 3 month data (long term and accelerated) for one full scale batch manufactured using (b) (4) -sourced drug substance.

Reviewer comments:

The product is a solution; thus, any differences in solid state characteristics between (b) (4) *and* (b) (4) *drug substance would not be relevant to stability. Reliance on stability data for product manufactured with* (b) (4) *drug substance batches is reasonable.* (b) (4) *The reviewer may consider requesting a statistical analysis for the* (b) (4) *stability data. Additionally, a shorter expiry may be required if the proposed limit for this impurity (NMT* (b) (4) *%) is not accepted by the nonclinical team.*

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications

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

B. FACILITIES*				
*	**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.**			
	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.**	X		
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		

	Parameter	Yes	No	Comment
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		Clarification of facility responsibilities requested. Additional information provided in 13-Jan-2014 amendment.
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		

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference to USP. As additional controls beyond USP monograph are needed, the acceptance specification for drug substance will be requested from applicant.
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Provided for f.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		EBR provided for Batch 915692 formulation, filling, sterilization, inspection and bulk packaging. MBR provided for formulation, filling, sterilization, inspection and bulk packaging operations.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Information is provided. The adequacy of the information is a review issue.
23.	Have any biowaivers been requested?		X	

	Parameter	Yes	No	Comment
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Information is provided. The adequacy of the information is a review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	X		

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Carbamazepine	11-Sep-2013	
	III		(b) (4)	03-Sep-2013	
	V			12-Nov-2013	
	III			11-Oct-2013	
	IV			22-Jan-2013	

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

BIOPHARMACEUTIC FILING REVIEW CHECKLIST

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

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	☐	☒	N/A
2.	Is the dissolution test part of the DP specifications?	☐	☒	N/A
3.	Does the application contain the dissolution method development report?	☐	☒	N/A
4.	Is there a validation package for the analytical method and dissolution methodology?	☐	☒	N/A
5.	Does the application include a biowaiver request?	☐	☒	The Applicant has conducted study OV-1015, which evaluates the relative bioavailability and pharmacokinetics of the proposed drug in adult epileptic patients. This study will be reviewed by the Clinical Pharmacology reviewer.
6.	Does the application include data supporting the biowaiver?	☐	☒	N/A
7. b	Does the application include an IVIVC model?	☐	☒	
8.	Is information such as BCS classification mentioned, and supportive data provided?	☐	☒	

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