

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022345Orig1s000**

**CHEMISTRY REVIEW(S)**

# **NDA 22-345 (POTIGA™) Resubmission**

**Ezogabine (formerly known as retigabine) Tablets**  
*Valeant Pharmaceuticals North America, Inc.*

**New Molecular Entity (NME)**

**Quality Review of NDA 22-345 Resubmission**

**Mohan K. Sapru, Ph.D.**

*Office of New Drug Quality Assessment*  
*Pre-Marketing Assessment Division I/Branch I*  
*Division of Neurology Products, HFD-120*

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**Chemistry Data Sheet**

- 1. NDA: 22-345 Resubmission.
- 2. REVIEW #: 2.
- 3. REVIEW DATE: 27-May-2011.
- 4. REVIEWER: Mohan K. Sapru, Ph.D.
- 5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

N/A

- 6. SUBMISSION(S) REVIEWED:

Submission (s) Reviewed	Document Date
NDA Class 1 Resubmission	15-April-2011

- 7. NAME & ADDRESS OF APPLICANT:

Name: Valeant Pharmaceuticals North America, Inc.  
 Address: One Enterprise, Aliso Viejo,  
 CA 92656, USA.

Representative: Susan T Hall, Ph.D.  
 Senior Vice President, R&D and Regulatory Compliance,  
 Valeant Pharmaceuticals North America, Inc.

Telephone: 919-294-3070

- 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Potiga Tablets.
- b) Non-Proprietary Name (USAN): Ezogabine
- c) INN: Retigabine.
- d) Code Name/ # (ONDQA only): N/A.
- e) Submission Classification: Class 1 Resubmission.

- 9. LEGAL BASIS FOR SUBMISSION: The application is a class 1 resubmission (S004) of NDA 22-345.

**Chemistry Data Sheet**

10. PHARMACOL .CATEGORY/ INDICATION: First in class neuronal potassium channel opener for the adjunctive anticonvulsant treatment of partial onset seizures in refractory epilepsy.
11. DOSAGE FORM: Immediate-release tablets.
12. STRENGTH/POTENCY: 50 mg, 200 mg, 300 mg, and 400 mg <sup>(b) (4)</sup>
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:   X   Rx       OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):  
   SPOTS Product – Form Completed.  
  X   Not a SPOTS Product.

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

IUPAC name: N-[2-Amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester.

BCS Classification: BCS II drug.

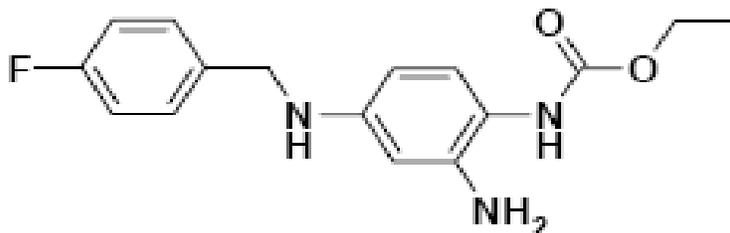
Molecular Formula: C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>2</sub>.

Molecular Weight: 303.3.

CAS No.: 150812-12-7.

Chemical Name: N-[2-Amino-4-(4-fluorophenyl-methylamino)-phenyl]carbamic acid ethyl ester.

Structure:



## The Executive Summary (NDA 22-345 Resubmission)

### I. Recommendations.

#### A. Recommendation and Conclusion on Approvability.

From the chemistry, manufacturing and controls (CMC) perspective, this resubmitted NDA for Potiga™ (ezogabine) tablets is recommended for approval.

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

Not applicable at this stage.

### II. Summary of Chemistry Assessments.

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

**Drug Substance:** The drug substance ezogabine (formerly known as retigabine), is a new molecular entity (NME), and is a first in class neuronal potassium channel opener for the treatment of partial-onset seizures. For detailed review of the drug substance, including *The Executive Summary*, refer to the original CMC review (review #1) for NDA 22-345.

**Drug Product:** The originally proposed drug product name i.e., retigabine tablets has been changed to ezogabine tablets. The proposed dosage form is an immediate-release, film-coated tablet, containing 50 mg, 200 mg, 300 mg, or 400 mg of ezogabine. With this NDA resubmission, the applicant has (b) (4)

(b) (4) For detailed review of drug product, including *The Executive Summary*, refer to the original CMC review (review #1) for NDA 22-345.

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

The drug product (ezogabine tablets) is to be used as the adjunctive treatment for partial-onset seizures in patients 18 years of age and older. Specifically, ezogabine is intended to be provided as an immediate-release, film-coated tablet in four different strengths i.e., 50 mg, 200 mg, 300 mg, and 400 mg. The recommended total daily dose of ezogabine is 600 to 1200 mg/day, given in a three times a day regimen. Ezogabine tablets will be packaged in (b) (4) plastic bottles and blisters. The bottle package is composed of opaque white round high density polyethylene (HDPE) bottles with white (b) (4) child-resistant caps and an induction seal liner. A cotton coil insert will be included in each bottle. All tablet strengths are packaged in 90-count bottles. (b) (4)

(b) (4)

The drug product stability data support an expiration period of 15 months for all tablet strengths (packaged in HDPE bottles or (b) (4) blisters) and not (b) (4), as proposed by the applicant. This conclusion is based upon the review of applicant's stability data, which reveal that all tablet strengths (packaged in HDPE bottles or (b) (4) blisters), don't meet specification for description beyond a period of 15 months when stored at long-term conditions i.e., 25°C/60% RH. Hence, CMC recommendation is to assign an expiration period of 15 months for all ezogabine tablet strengths (packaged in HDPE bottles or (b) (4) blisters) with storage at 25°C and excursions permitted to 15-30°C.

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

In alliance with its development partner GlaxoSmithKline (GSK), the applicant, Valeant Pharmaceuticals North America, Inc., has sought marketing approval of Potiga™ (ezogabine) tablets for the adjunctive treatment for partial-onset seizures in patients 18 years of age and older. Valeant Pharmaceuticals submitted a New Drug Application (NDA 22-345) to the Agency on October 30, 2009. Following a multidisciplinary review, the Agency issued a Complete Response letter for NDA 22-345 on November 30, 2010. While no clinical deficiencies were identified, however, the Agency communicated to the applicant that NDA 22-345 is not approved due to the high acceptance limit proposed for the mutagenic impurity (b) (4) which was originally set at not more than (b) (4). For a detailed review of drug substance impurities, including the mutagenic impurity (b) (4), refer to the original CMC review (review #1) for NDA 22-345.

Specifically, the (b) (4) impurity, a (b) (4), harbors an (b) (4) for mutagenicity, and has been reproducibly found to be positive in the *in vitro* Ames test. Although (b) (4) was found to be negative when tested *in vivo* in a combined rat micronucleus and Comet assay, however, the Pharmacology/Toxicology review team determined that these results do not provide a basis for dismissing the mutagenic potential clearly demonstrated in the Ames assay. Furthermore, the review team noted that the Ames assay and the *in vivo* assays evaluate different genotoxicity endpoints that do not always correlate and, at this time, there are inadequate data to determine whether a negative Comet assay has adequate negative predictive value to provide reassurance in the face of a positive Ames test. Therefore, the Agency via a Complete Response letter (November 30, 2010) communicated that the applicant will need to lower the acceptance limit to one that results in a daily dose of (b) (4) which is considered acceptable for a genotoxic impurity. (b) (4)

As described in the NDA 22-345 resubmission, the applicant has addressed the deficiency concerning acceptance limit for genotoxic impurity, (b) (4) by slightly modifying the drug substance manufacturing process, thereby, lowering the (b) (4) impurity levels to a level of (b) (4) which is equivalent to (b) (4) based on a maximum daily dose of 1200 mg.

Specifically, lowering of the (b) (4) impurity has been achieved by (b) (4)

No new organic solvents have been introduced into the manufacturing process. Furthermore, the applicant has demonstrated that the physical and chemical characteristics, including polymorphic form, particle size distribution and stability of the drug substance are unaffected by the minor modification to the manufacturing process. In addition, the analytical method for determination of (b) (4) content by HPLC mass spectrometry (LCMS) has been validated for specificity, linearity, repeatability, precision and accuracy, and is capable of quantifying at the new acceptance level of NMT (b) (4). Based on the Biopharmaceutics review of original NDA 22345, the Agency expressed concerns about dissolution data provided for (b) (4). As a result, the Agency accepted a biowaiver for all tablet strengths (b) (4). Addressing this deficiency, the applicant, via this NDA resubmission, (b) (4) has agreed to only market the 50 mg, 200 mg, 300 mg, and the 400 mg tablet strengths. Furthermore, in response to the Agency's concerns about the dissolution method, the applicant has tightened the dissolution specification to Q= (b) (4) in 15 minutes (from Q= (b) (4) in 30 minutes). The batch analysis and *in vitro* dissolution data concerning ezogabine tablets, manufactured using the drug substance synthesized by the modified commercial process, provide confirmatory evidence that the proposed minor modification to the drug substance manufacturing process does not affect the critical attributes of the drug product.

From the CMC perspective, there are no outstanding labeling-related issues. Lastly, since the commercial drug substance manufacturing site (b) (4) has already been inspected as part of the preapproval inspection process and deemed to have adequate cGMP compliance, the NDA resubmission would not require another inspection of the facility to support the minor change to the drug substance synthetic process. In conclusion, since the applicant has satisfactorily addressed all the identified deficiencies, from the CMC perspective, this resubmitted NDA for Potiga™ (ezogabine) tablets is recommended for approval.

### III. Administrative.

#### A. Reviewer's Signature

*Mohan Sapru*

#### B. Endorsement Block

Review Chemist: Mohan K. Sapru, Ph.D.  
CMC Lead: Martha Heimann, Ph.D.  
Chemistry Team Leader: Ramesh Sood, Ph.D.

#### C. Block

Project Manager: Karen Abraham-Burrell, Pharm.D.

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/s/  
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MOHAN K SAPRU  
06/01/2011

RAMESH K SOOD  
06/02/2011

**ONDQA Division Director's Memo**  
**NDA 22-345, POTIGA™ (ezogabine) Tablets,**  
**50 mg, (b) (4) 200mg, 300 mg and 400mg**  
***immediate release, film-coated, tablets***  
**Date: 29-NOV-2010**

**Introduction**

Ezogabine tablets are indicated for adjunct therapy in refractory epilepsy patients with partial-onset seizures. Ezogabine tablets are proposed to be administered in three doses per day. The recommended total daily dose of ezogabine is 600 mg to 1200 mg per day.

**Administrative**

This is a standard-clock NME NDA submission (1S) submitted by Valeant Pharmaceuticals North America, Inc., of Aliso Viejo, CA. In addition to the original submission (30-OCT-2009), a total of five amendments (received 17-FEB-2010 through 07-JUL-2010) were reviewed. The NDA is supported by nine Drug Master files (DMFs) and IND 53,950. **The clock was extended on this NDA; but not for reasons involving CMC.**

An overall acceptable recommendation was received from The Office of Compliance on 19-APR-2010. Other consults and related reviews include Environmental Assessment (categorical exclusion 15-AUG-2010), Biopharmaceutics (biowaiver issue resolved. 13-AUG-2010), and Pharmacology/Toxicology (**pending** as of this writing).

**ONDQA recommends approval from the CMC perspective provided the currently proposed limit of (b) (4) for [genotoxic] impurity (b) (4) is considered to be acceptable per the Pharmacology Toxicology review (pending).**

See “REMAINING ISSUE(s) AFFECTING APPROVABILITY”, below.

**Drug Substance: Ezogabine**

The drug substance ezogabine, is a new molecular entity (NME). It is a non-hygroscopic white to slightly colored powder with very poor solubility in water. The low solubility and high permeability of ezogabine follows a class II biopharmaceutics drug classification system (BCS).

Ezogabine exhibits five polymorph forms. (b) (4)

**Genotoxic impurities:** (b) (4) a known mutagen (b) (4) and (b) (4) and (b) (4) (also known as

(b) (4) A series of validated analytical methods have been developed for determining the residual levels of all the identified impurities in the drug substance.

The primary long-term and accelerated stability data for four batches of drug substance, manufactured using the (b) (4) reveal no significant changes in drug substance following storage: a) at 5°C, 25°C/60% RH for a period of up to 18 months, or b) under accelerated conditions of 40°C/75% RH for a period of 6 months. Supportive long-term and accelerated stability data for three batches of (b) (4) drug substance, manufactured using the improved commercial process, show that there are no significant changes in drug substance following storage at 25°C/60% RH or under accelerated conditions of 40°C/75% RH for a period of 3 months.

IUPAC name: N-[2-Amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester

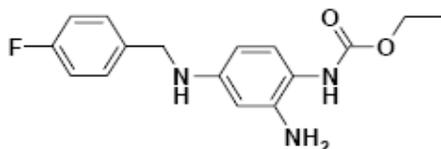
Molecular Formula: C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>2</sub>

Molecular Weight: 303.3

CAS No.: 150812-12-7

Chemical Name: N-[2-Amino-4-(4-fluorophenyl-methylamino)-phenyl]carbamic acid ethyl ester

Structure:



### **Drug Product: Ezogabine Tablets**

**Drug Product:** The dosage form is immediate-release, film-coated tablets containing 50 mg, (b) (4), 200 mg, 300 mg, or 400 mg of ezogabine. The five strengths of tablets are differentiated by a combination of size, color, debossing, and shape.

Ezogabine tablets are manufactured (b) (4)

(b) (4) With the exception of (b) (4) film coats (b) (4), adequate), all the excipients used meet the compendial (USP/NF) requirements.

Ezogabine tablets are packaged in high density polyethylene (HDPE) bottles and (b) (4) blisters. Based on stability data, ezogabine tablets of all the five different strengths (50, (b) (4) 200, 300, and 400 mg) packaged in HDPE bottles or (b) (4) blisters show acceptable stability following storage at the long-term condition

(25°C/60% RH) up to a period of 15 months. **An expiration period of fifteen (15) months at 25°C (excursions permitted to 15-30°C) for all strengths of ezogabine tablets at 25°C in 90-count HDPE bottles and blisters is allowable at this time**

### **REMAINING ISSUE(s) AFFECTING APPROVABILITY**

No additional impurities beyond those already identified in the drug substance (b) (4) are found in the drug product.

As of 16-NOV-2010 (internal review team meeting), the remaining genotoxic impurity issue is for (b) (4). The applicant proposes (b) (4) (revised from earlier (b) (4)) which is consistent with their current production capability based on batch results.

However, it appears that based on a human exposure concern of less than (b) (4), Pharmacology/Toxicology may require the level of this impurity to be reduced to (b) (4) (based on the maximum recommended daily dose) owing to toxicological concerns (not CMC). Therefore, if this issue persists as the basis for a CR recommendation it is **not** a CMC deficiency.

Rik Lostritto, Ph.D., Director, ONDQA Division I.

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/s/  
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RICHARD T LOSTRITTO  
11/29/2010

# **NDA 22-345 (POTIGA™)**

**Ezogabine (Formerly Known as Retigabine) Tablets  
Valeant Pharmaceuticals North America, Inc.**

## **Quality Review #1**

**Mohan K. Sapru, Ph.D.**

*Office of New Drug Quality Assessment  
Pre-Marketing Assessment Division I/Branch I  
Division of Neurology Products, HFD-120*

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## Chemistry Review Data Sheet

1. NDA: 22-345
2. REVIEW #: 1
3. REVIEW DATE: 27-Aug-2010
4. REVIEWER: Mohan K. Sapru, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N/A	N/A

## 6. SUBMISSION(S) REVIEWED:

<u>Submission (s) Reviewed</u>	<u>Document Date</u>
<u>Original Submission</u>	30-October-2009
Amendment-11	17-Feb-2010
Amendment-16	24-March-2-10
Amendment-24	04-June-2010
Amendment-25	21-June-2010
Amendment-28	07-July-2010

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Valeant Pharmaceuticals North America, Inc.  
Address: One Enterprise, Aliso Viejo, CA 92656, USA

Representative: Susan T Hall, Ph.D.  
Head of Neurology R&D and Regulatory Compliance  
Valeant Pharmaceuticals North America, Inc.

Telephone: 919-294-3070

## 8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: Potiga™
- b) Non-Proprietary Name (USAN): Ezogabine (formerly known as Retigabine)
- INN: Retigabine
- Code Name/ # (ONDQA only): N/A

## c) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The application was submitted under Section 505(b) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.50

10. PHARMACOL. CATEGORY/INDICATION: Neuronal potassium channel opener for the adjunctive anticonvulsant treatment of partial onset seizures in refractory epilepsy

11. DOSAGE FORM: Immediate-release tablets

12. STRENGTH/POTENCY: 50 mg, (b) (4), 200 mg, 300 mg, and 400 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:   X   Rx       OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

   SPOTS product – Form Completed  
  X   Not a SPOTS product

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

IUPAC name: N-[2-Amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester

Molecular Formula: C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>2</sub>

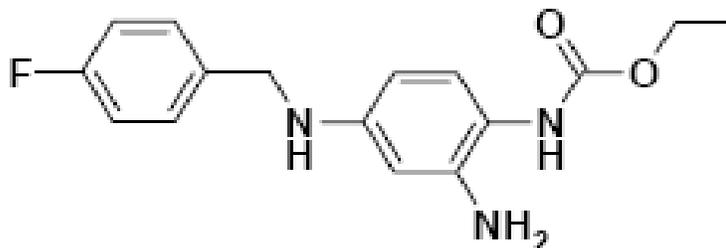
## Chemistry Review Data Sheet

Molecular Weight: 303.3

CAS No.: 150812-12-7

Chemical Name: N-[2-Amino-4-(4-fluorophenyl-methylamino)-phenyl]carbamic acid ethyl ester

Structure:



## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	20-March-2010 17-April-2010
	III			3	Adequate	23-Feb-2010
	III			3	Adequate	10-July-2006
	III			3	Adequate	12-July-2004
	III			7	N/A	Adequate information in the application
	III			3	Adequate	11-Dec-2007
	III			3	Adequate	09-Feb-2009
	III			3	Adequate	09-March-2010
	III			3	Adequate	16-July-2004

## Chemistry Review Data Sheet

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	53,950	Adjunctive anticonvulsant treatment of partial onset seizures in refractory epilepsy

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	19-APR-2010	M. Stock
Methods Validation	Not requested. The methods are conventional and don't qualify for internal validation by the FDA laboratories.	-	Mohan Sapru, Ph.D.
Environmental Assessment	Categorical Exclusion		Mohan Sapru, Ph.D.
Biopharmaceutics	Biowaiver issue is unresolved	13-Aug-2010	John Duan, Ph.D.
Pharmacology/Toxicology	Pending	-	Edward Fisher, Ph.D.
Microbiology	N/A	N/A	N/A

## Executive Summary Section

**The Executive Summary (NDA 22-345)****I. Recommendations.****A. Recommendation and Conclusion on Approvability**

From the chemistry, manufacturing and controls (CMC) perspective, this NDA for ezogabine tablets (formerly known as retigabine tablets) cannot be recommended for approval unless the unresolved deficiency regarding the high levels of potentially genotoxic impurity (b) (4) in the active pharmaceutical ingredient (API) is satisfactorily addressed. The (b) (4) impurity, which harbors an (b) (4) for mutagenicity, has been found to be positive in the *in vitro* Ames test. Given the applicant's apparent inability or unwillingness to tighten the acceptance limits for the (b) (4) impurity, the CMC reviewer sought an assessment from the Pharmacology/Toxicology review team about the genotoxicity of this impurity. In addition, the Pharmacology/Toxicology review team was approached to specify the combined level for the identified genotoxic impurities (other than (b) (4) that would be acceptable, based on analysis of the applicant's toxicological qualification data. Since a final assessment and recommendations concerning these issues are still awaited from the Pharmacology/Toxicology review team, the CMC reviewer cannot make a final recommendation concerning approval of this NDA. If the Pharmacology/Toxicology review team makes a final assessment of classifying the (b) (4) impurity as a genotoxic impurity and considers it unacceptable to have the identified genotoxic impurities present at levels higher than the combined limit of (b) (4) then the CMC recommendation to the applicant will be to eliminate the (b) (4) impurity either by introducing (b) (4) in the API synthetic pathway and/or to (b) (4) involved in the API synthesis. Lastly, the Biopharmaceutics review of the applicant's comparative dissolution data does not, at this stage, adequately support granting an *in vivo* bioequivalence waiver for the lower strengths of the market image tablets i.e., 50 mg, (b) (4) 200 mg, and 300 mg.

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

Not applicable at this stage.

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

**Drug Substance:** The drug substance ezogabine (formerly known as retigabine), a new molecular entity (NME), is non-hygroscopic white to slightly colored powder with very poor solubility in water. (b) (4)

(b) (4). The structure of ezogabine, which has been adequately characterized by elemental analysis, mass spectroscopy, <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) spectroscopy, X-ray crystal structure, ultraviolet (UV) and infrared (IR) spectroscopy,

## Executive Summary Section

harbors a (b) (4) for mutagenicity. The primary pharmacological property of ezogabine is to enhance the neuronal  $K^+$  current mediated by the Kv7 subfamily of voltage-gated potassium (KCNQ) channels. The drug substance manufacturing process is composed of (b) (4). While no (b) (4) has been used for the preparation of Phase III clinical batches, the manufacture of four primary stability batches has involved (b) (4). However, manufacture of the commercial batches has involved the introduction of (b) (4) process as process improvements. The previously used (b) (4) and the newly introduced (b) (4) for commercial manufacturing, however, consistently produce the (b) (4) drug substance. Regarding the genotoxic impurities, (b) (4) a known mutagen, is (b) (4). In addition, two (b) (4) have been found to be positive in the *in vitro* Ames test. A series of validated analytical methods have been developed for determining the residual levels of all the identified impurities in the drug substance. No materials of human or animal origin are used in the manufacture of ezogabine. The primary long-term and accelerated stability data for four batches of drug substance, manufactured using the (b) (4), reveal no significant changes in drug substance following storage: a) at 5°C, 25°C/60% RH for a period of up to 18 months, or b) under accelerated conditions of 40°C/75% RH for a period of 6 months. Supportive long-term and accelerated stability data for three batches of (b) (4) drug substance, manufactured using the improved commercial process, show that there are no significant changes in drug substance following storage at 25°C/60% RH or under accelerated conditions of 40°C/75% RH for a period of 3 months.

**Drug Product:** It is important to note that the originally proposed drug product name i.e., retigabine tablets, has recently been changed to ezogabine tablets. The proposed dosage form is immediate-release, film-coated tablet containing 50, (b) (4) 200, 300, and 400 mg of ezogabine (retigabine). The five strengths of ezogabine tablets are differentiated by a combination of size, color and shape. The 200 mg and 400 mg tablets have not been used in clinical trials. Each proposed commercial tablet is debossed to identify and differentiate the unit dose strength. The tablet formulations have been optimized by systematic investigations of various excipients, such as, (b) (4). Ezogabine tablets are manufactured using a (b) (4), followed by (b) (4). With the exception of (b) (4), all the excipients used meet the compendial (USP/USNF) requirements. A list of the components in the (b) (4) has been provided and details cross-referenced to the drug master file (b) (4), which has previously been reviewed and found to be adequate by the agency. All excipients are tested in accordance with the current monograph in the relevant pharmacopoeia. The low solubility and high permeability of ezogabine follows a class II biopharmaceutics drug classification system (BCS). In conformity with compendial standards, the applicant has used two different analytical tools i.e., HPLC and ultraviolet spectroscopy as dual tests for identification of drug substance in ezogabine tablets. The analytical procedures used have been validated to meet the general requirements of the ICH Guideline, Q2 (R1). Furthermore, the applicant has carried out detailed validation of analytical procedures to demonstrate the suitability of each procedure for its intended purpose. Regarding drug product batch analysis, it is important to note that no additional impurities beyond those already identified in the drug

## Executive Summary Section

substance are found in the drug product. Ezogabine tablets are packaged in high density polyethylene (HDPE) bottles and (b) (4) blisters. Based on stability data, ezogabine tablets of all the five different strengths (50, (b) (4) 200, 300, and 400 mg) packaged in HDPE bottles or (b) (4) blisters show acceptable stability following storage at the long-term condition (25°C/60% RH) up to a period of 15 months. (b) (4)

(b) (4) Taken together, the stability studies involving non-commercial pilot batches support storage of ezogabine tablets at 25°C in 90-count HDPE bottles and blisters (excursions permitted to 15-30°C) with an expiration period of 15 months applied to all tablet strengths in either 90-ct bottles or blisters.

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

Ezogabine is intended to be provided as an immediate-release, film-coated tablet in five different strengths i.e., 50, (b) (4), 200, 300, and 400 mg. As an adjunct therapy for refractory epilepsy patients with partial-onset seizures, ezogabine tablets are proposed to be administered in 3 divided doses daily. The recommended total daily dose of ezogabine is 600 to 1200 mg/day.

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

Regarding the profile of genotoxic impurities in the active pharmaceutical ingredient (API), (b) (4) a known mutagen, is (b) (4). In addition, (b) (4) a (b) (4) has been found to be positive in the *in vitro* Ames test. Both if these impurities have been classified as genotoxic impurities by the applicant, and are appropriately controlled in the API to a combined limit of Not More Than (NMT) (b) (4) which is equivalent to (b) (4) based on a maximum daily dose of 1200 mg. However, the major safety concern regarding this NDA stems from the presence of high levels of the (b) (4) impurity in the API. Specifically, the (b) (4) impurity, a (b) (4) harbors an (b) (4) for mutagenicity, and has been found to be positive in the *in vitro* Ames test. The acceptance limit for the (b) (4) impurity is set at (b) (4), which is equivalent to 240 ug/day based on a maximum daily dose of 1200 mg. During the 04-Aug-2009 pre-NDA meeting, the Agency recommended that the applicant continue efforts to reduce levels of (b) (4) impurity to an exposure level of (b) (4). However, despite a few modifications introduced in the commercial manufacturing process, the applicant has not been able to eliminate the (b) (4) process impurity or significantly bring down its levels in the API so that the combined limit of all the identified genotoxic impurities stays within the acceptable range of (b) (4) for long-term administration of ezogabine (retigabine) tablets. During the review process, the CMC reviewer recommended to the applicant that the acceptance limits for the (b) (4) impurity in the API be considerably tightened. In response (amendment 25 dated June-21-2010), the applicant has stated that “tightening the acceptance limit in the

## Executive Summary Section

absence of additional data at full commercial scale could compromise our ability to manufacture drug substance that will consistently comply with a tighter acceptance limit and could impact continuity of supply". So this major deficiency regarding the levels of (b) (4) impurity in the API remains unresolved. Given the applicant's unwillingness to tighten the acceptance limits for the (b) (4) impurity, an assessment from the Pharmacology/Toxicology review team about the genotoxicity status of this impurity was sought. In addition, the Pharmacology/Toxicology review team was approached to specify the combined level for the identified genotoxic impurities (other than (b) (4)) that would be acceptable based on the analysis of the applicant's toxicological qualification data. Though the Pharmacology/Toxicology review team considers the (b) (4) impurity as a genotoxic impurity based on positive Ames test results (refer to page 126), however, a final assessment and recommendations concerning these issues are still awaited from the Pharmacology/Toxicology review team. If the Pharmacology/Toxicology review team makes a final assessment of classifying the (b) (4) impurity as a genotoxic impurity and considers the presence of identified genotoxic impurities above a combined level of NMT (b) (4) unacceptable, then the CMC recommendation to the applicant will be to eliminate the (b) (4) impurity either by introducing additional purification steps in the (b) (4). Lastly, the Biopharmaceutics review of the applicant's comparative dissolution data does not, at this stage, adequately support granting an *in vivo* bioequivalence waiver for the lower strengths of the market image tablets i.e., 50 mg, (b) (4), 200 mg, and 300 mg. For details regarding this unresolved deficiency, refer to the Biopharmaceutics review by Dr. John Duan. In conclusion, the applicant will need to satisfactorily address the unresolved deficiencies concerning the dissolution method used, and the comparative dissolution data generated to support an *in vivo* bioequivalence waiver request for the lower strengths of the market image tablets i.e., 50 mg, (b) (4) 200 mg, and 300 mg. In addition, we are still awaiting a final recommendation from the Pharmacology/Toxicology reviewer regarding the genotoxicity issue concerning the impurity (b) (4) in the API.

### III. Administrative.

#### A. Reviewer's Signature

*Mohan Sapru*

#### B. Endorsement Block

Review Chemist:	Mohan K. Sapru, Ph.D.
CMC Lead	Martha Heimann
Chemistry Team Leader:	Ramesh Sood, Ph.D.

#### D. CC Block

Project Manager:	Stephanie N. Keefe
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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

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/s/

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MOHAN K SAPRU  
08/30/2010

RAMESH K SOOD  
08/30/2010

Initial Quality Assessment  
Branch I  
Pre-Marketing Assessment Division I

**OND Division:** Division of Neurology Products  
**NDA:** 22-345  
**Applicant:** Valeant Pharmaceuticals North America  
**Stamp Date:** 30-Oct-2009  
**PDUFA Date:** 30-Aug-2010  
**Trademark:** Potiga is proposed  
**Established Name:** retigabine  
**Dosage Form:** Tablets  
**Route of Administration:** Oral  
**Indication:** Epilepsy

**PAL:** Martha R. Heimann, Ph.D.

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

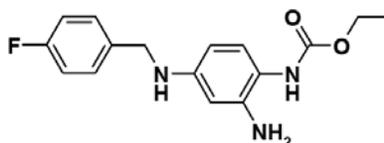
## Summary and Critical Issues:

### *Summary*

Retigabine (GKE-841 or GW582892X) is a new molecular entity that was developed by Valeant Pharmaceuticals for use as adjunctive therapy in epilepsy patients with partial-onset seizures. It is a first in class, orally active, neuronal potassium channel opener. Valeant, in partnership with GlaxoSmithKline, proposes marketing of retigabine as immediate release tablets containing 50 mg, (b) (4), 200 mg, 300 mg, or 400 mg retigabine. The recommended dose is 600 mg to 1200 mg per day, given as 3 divided doses.

### Drug Substance

The active ingredient, retigabine [N-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester], is a small molecule with molecular formula C<sub>16</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>2</sub> and molecular weight 303.3. The structural formula for retigabine is:



Retigabine is practically insoluble (0.04 to 0.05 mg/mL) in water or aqueous media above pH 5 and sparingly soluble (16 mg/mL) in 0.1 N HCl. It has a pKa of 3.7. The drug substance is non-hygroscopic. (b) (4)

The bulk drug substance is designated as [REDACTED] (b) (4)

Retigabine is manufactured by [REDACTED] (b) (4) at the firm's [REDACTED] (b) (4) facility. The proposed commercial manufacturing process is outlined in Figure 1 below:

**Figure 1: Flow Chart for the Synthesis of Retigabine**



It is noted that there are a number of differences between the commercial manufacturing process and the process used for manufacture of clinical and primary stability batches. The differences between the clinical manufacturing process and the commercial process are summarized in Figure 2 on the following page. The applicant considers all changes "minor in nature."

(b) (4)



The changes from the clinical/primary stability batch manufacturing process to the commercial process include a change at (b) (4) from a (b) (4). During the pre-NDA meeting held on 04-Aug-2009, the applicant sought Agency concurrence that

stability data generated using clinical/primary stability batches would support the commercial process. The applicant was advised that the Agency did not consider the change to the (b) (4) described above to be a minor change; however, the existing stability database would be reviewed in support of the proposed retest period. The applicant was also advised to provide comparative dissolution profile data for the drug product manufactured using drug substance obtained from the (b) (4) versus the drug product used in clinical studies and manufactured using drug substance obtained using the (b) (4). The applicant has provided comparative dissolution profiles for the highest strength tablet (400 mg) in the Pharmaceutical Development Section [3.2.P.2.2.1, Figure 1] but has not provided the individual tablet data for review. The data will be requested in the 74-Day letter. No dissolution data are provided for the lower tablet strengths. The sponsor will be asked to provide data for the lowest tablet strength.

The proposed specification for retigabine is shown in Table 1 below. The proposed analytical procedures for retigabine are straight-forward. Two related reverse phase HPLC methods are used for assay and determination of ordinary related substances. Three potentially genotoxic impurities are controlled by LC-MS procedures.

**Table 1: Proposed Specification for Retigabine**

Test	Acceptance Criteria	Method
(b) (4)		

With respect to the proposed specification, the following concerns are noted:

The impurities (b) (4) were previously identified by the applicant as Ames positive and a known mutagen, respectively. [27-Feb-2009 submission to IND 53,950] In the same IND submission, the (b) (4) impurity was identified as potentially genotoxic. Based on structure activity relationship (SAR) considerations, the applicant proposed a limit of (b) (4). During the 04-Aug-2009 pre-NDA meeting the Agency recommended that the applicant continue efforts to reduce levels of this impurity to an exposure level (b) (4). Given the highest proposed daily dose for retigabine, 1200 mg/day, the (b) (4) corresponds to NMT (b) (4) in the bulk drug substance. The reviewer should consult with the Pharm/Tox reviewer to determine the acceptability of the proposed (b) (4) limit.

(b) (4)

The NDA stability package includes long term stability data through 18 months and accelerated data through 6 months for 4 batches of retigabine drug substance. All batches are pilot scale and were manufactured by (b) (4) at the proposed commercial facility. As noted above, however, the primary stability batches were manufactured by the clinical process (b) (4) rather than the commercial process (b) (4). The applicability of the existing stability database to support the proposed retest period (b) (4) is deferred to the primary reviewer. The sponsor will be asked to clarify whether drug substance from the (b) (4) has been placed on stability and to provide any available stability data.

Drug Product

The proposed dosage form is an immediate release, film-coated tablet containing 50 mg, (b) (4) 200 mg, 300 mg, or 400 mg of retigabine. The tablet presentations are summarized in Table 2. Retigabine tablets will be packaged in 90 count HDPE bottles and (b) (4) blisters.

**Table 2: Retigabine Tablets Physical Description**

Tablet Strength (mg)	Color	Size/Shape (tablet tooling dimensions)	Compression Weight (core tablets)	Debossing (one tablet side only)
50	Purple	0.22 inch round	(b) (4)	RTG 50
		(b) (4)		(b) (4)
200	Yellow	0.28 x 0.55 inch oblong		RTG-200
300	Green	0.28 x 0.63 inch oblong		RTG-300
400	Purple	0.32 x 0.71 inch oblong		RTG-400

The quantitative formulations for retigabine tablets are summarized in Table 3. Retigabine tablet cores are (b) (4)

**Table 3: Retigabine Tablet 50, (b) (4) 200, 300, and 400 mg Composition**

Component	Reference to Standards	Function	Composition in mg per Tablet (% w/w)				
			50 mg	(b) (4)	200 mg	300 mg	400 mg
<b>Tablet Cores</b>							
Retigabine	Internal	Drug Substance	50.0 (62.5%)	(b) (4)	200.0 (62.5%)	300.0 (62.5%)	400.0 (62.5%)
Microcrystalline cellulose	USNF/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hypromellose, 2910	USP/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Croscarmellose sodium	USNF/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium stearate	USNF/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<b>Theoretical Uncoated Tablet Weight</b>						(b) (4)	
<b>Film Coat<sup>b</sup></b>							
(b) (4)	Internal	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Internal	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Internal	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP/ Ph. Eur.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
<b>Theoretical Coated Tablet Weight</b>						(b) (4)	

<sup>a</sup> Removed during processing  
<sup>b</sup> Amounts in table reflect a (b) (4) weight gain. A range of (b) (4) weight gain is acceptable.  
 q.s. Add sufficient amount

Tablet excipients are typical ingredients for solid oral dosage forms and all excipients except the (b) (4) film coats comply with compendial requirements. The proposed commercial tablet core formulations for the 50 mg, (b) (4) and 300 mg strengths are quantitatively identical to tablet cores used for the clinical studies. Differences between the clinical tablets and the proposed commercial 50 mg, (b) (4) and 300 mg tablets are limited to film coat formulation and color, tablet shape and debossing. 200 mg and 400 mg tablets were not used in clinical trials.

The applicant has performed a bioequivalence study (Study VRX-RET-E22-105) comparing the commercial formulation (400 mg tablet) to the clinical formulation (1 x 300 mg plus 2 x 50 mg). In this study the retigabine market image tablet was equivalent to the clinical trial tablet on the basis of overall systemic exposure (AUC), but not C<sub>max</sub>. The upper end of the 90% confidence interval (133%) for the peak concentration (C<sub>max</sub>) exceeded the traditional acceptance range for equivalence (125%) and the geometric mean of the market image tablet was 16% higher than that of the clinical trial tablet. Interpretation of the bioequivalence results is deferred to the Office of Clinical Pharmacology. The following points are noted however with respect to comparability of the clinical and market image formulations:

The applicant attributes the nonequivalence for Cmax to differences in particle size between the drug substance batches used to manufacture the clinical batches and the drug substance batch (Lot #02070069) used to manufacture the "market image" 400 mg tablet. The applicant, however, fails to note that the drug substance lot used to manufacture "market image" was manufactured by the clinical/primary stability batch process (b) (4) rather than by the proposed commercial process (b) (4).

Regardless of the results from Study VRX-RET-E22-105, the applicant has not submitted either bioequivalence data to support the lower strengths of the market image tablets or a biowaiver request for the lower strengths. No comparative dissolution profile data that would support a biowaiver request for the lower strengths could be located during the initial assessment of the application.

Retigabine tablets will be manufactured by (b) (4) at the firm's (b) (4) facility. The tablets are manufactured using the following unit operations: (b) (4)

During manufacturing process development, the applicant evaluated the typical process parameters for each of these unit operations using a traditional (non QbD) approach to evaluate process parameters.

The proposed regulatory specification for Retigabine Tablets is shown in the following page. Test parameters are typical for an immediate release tablet and the analytical methods are straightforward. HPLC methods used for assay, identification and determination of related substances are essentially the same as for the bulk drug substance. The proposed dissolution test parameters are USP Apparatus 2 at RPM, 1000 mL 0.01 N HCl dissolution medium, sampling at 30 minutes, and assay by UV at 293 nm.

**Table 4: Specifications for Retigabine Tablets (50 (b) (4) 200, 300 and 400 mg)**

Test	Acceptance Criteria	Method
<b>Description</b>	<b>50 mg tablet:</b> round purple film coated tablet with debossed "RTG 50" on one side (b) (4)	Visual observation
	<b>200 mg tablet:</b> oblong yellow film coated tablet with debossed "RTG-200" on one side	
	<b>300 mg tablet:</b> oblong green film coated tablet with debossed "RTG-300" on one side	
	<b>400 mg tablet:</b> oblong purple film coated tablet with debossed "RTG-400" on one side	
<b>Identification by HPLC</b>	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the retigabine reference standard.	HPLC
<b>Identification by UV</b>	Spectrum conforms to reference (b) (4)	UV
<b>Assay (% of Label Claim)</b>	(b) (4)	HPLC
<b>Related Impurities (% w/w)</b>		
Any unspecified impurity	(b) (4)	HPLC
Total impurities <sup>1</sup>	(b) (4)	
<b>Uniformity of Dose</b>	Meets USP criteria	USP <905>; weight variation
<b>Dissolution</b>	Meets USP criteria, Q- (b) (4) at 30 min	USP apparatus 2 with UV detection

## NOTES:

RT = retention time

NMT = not more than

1. Includes process impurities and degradation products

The NDA stability package includes long term stability data for through 18 months and accelerated stability data through 6 months for pilot scale batches of retigabine tablets. The applicant employs a bracketing approach. Stability data are provided for three batches each of the highest and lowest tablet strengths (50 mg and 400 mg) and one batch of each intermediate strength retigabine (b) (4) 200 mg, 300 mg). All stability batches were packaged in HDPE bottles and (b) (4) blisters that are representative of the proposed commercial packaging configurations. It is noted that the primary drug product stability batches were manufactured using drug substance manufactured by the clinical batch process (b) (4) rather than by the proposed commercial process. The sponsor will be asked to provide any available stability data representative of the (b) (4) in the 74-Day letter.

***Critical issues for review******Impurities***

As discussed above, the drug substance manufacturing process involves three potentially genotoxic compounds, (b) (4). Controls for these impurities should be assessed in consultation with the Pharm/Tox reviewer.

*Drug substance particle size*

Drug substance particle size, i.e., (b) (4) particle size fractions have been shown to affect the rate of tablet dissolution and potentially bioavailability. It is noted that the applicant implicates drug substance particle size when attempting to interpret the results of bioequivalence study VRX-RTG-E22-105, in which the market image 400 mg tablet failed to meet BE criteria for C<sub>max</sub>. [Refer to Section P.2.2] The applicant's justification for the proposed particle size acceptance criteria should be examined carefully.

*Drug substance solid state form*

The drug substance exhibits polymorphism. Two process parameters, i.e. (b) (4) (b) (4) are identified as critical to control formation of the desired form, (b) (4). Information to support the controls should be requested in the 74-Day letter and evaluated carefully by the reviewer.

The applicant has provided IR and X-ray powder diffraction data to demonstrate that the different polymorphs can be distinguished by both techniques and both tests are included in the drug substance specification to confirm identity of (b) (4). The applicant does not, however, propose limits for other polymorphic forms, or amorphous material in the bulk drug substance. Retigabine has limited solubility in aqueous media and the control of other polymorphic forms in the drug substance may be critical to bioavailability of the drug product. The applicant should, therefore, be asked to provide justification for the absence of this control. This should be communicated in the 74-Day letter.

As discussed above, the change from a (b) (4) process to (b) (4) has the potential to impact bioavailability of the resulting drug product. Although the (b) (4) process produces the same polymorphic form, (b) (4) the supporting data for equivalence of the two processes should be evaluated carefully to verify that the analytical procedures used are capable of detecting small amounts of other polymorphs or amorphous materials.

(b) (4)

*Clinical vs. market image formulation*

A number of changes are made between the clinical and commercial drug product. The changes include:

- Addition of two tablet strengths, 200 mg and 400 mg, not used in clinical studies

(b) (4)

- Addition of debossing to the commercial tablets
- Change in film coat composition from a (b) (4) based formulation to a (b) (4) based formulation with change in colorants.
- Change from (b) (4) drug substance to (b) (4) drug substance

Although the changes to tablet shape, film-coating and addition of debossing might not be expected to impact on product quality; the change in the drug substance manufacturing process from a (b) (4) process to (b) (4) has the potential to affect bioavailability of the resulting drug product. (b) (4)

The bioequivalence study intended to support the market image 400 mg tablets was performed using a tablet batch manufactured from (b) (4) (clinical) drug substance rather than (b) (4) drug substance. Thus, it is not clear that the 400 mg tablet bioequivalence batch is representative of the commercial product. It is recommended that this point be discussed with the Clinical Pharmacology reviewer.

Linkage between the 400 mg bioequivalence batch and commercial product manufactured from (b) (4) drug substance may be established by comparative dissolution testing. It is recommended that the ONDQA Biopharmaceutics review staff be consulted for review of supporting dissolution documentation.

The applicant will need to submit either a formal biowaiver request for the lower tablet strengths or supporting bioequivalence data. This should be communicated in the 74-Day letter.

### ***Additional issues***

*Administrative:* The applicant's claim for categorical exclusion from environmental assessment under 21 CFR 25.31(b) is included in Module 1 of the application.

*Establishment Evaluation:* All required establishment information is provided as an addendum to the Form 356h. The commercial facilities listed in Attachment 1 were submitted for Compliance evaluation on 05-Nov-2009.

*Labeling/Established Name:* The active ingredient, retigabine, is the free base. Thus, there are no issues related to consistency between the established name "retigabine tablets" and labeled potency.

### ***Comments for 74-Day Letter***

With regard to the drug substance manufacturing process, you identify two process parameters, i.e. (b) (4) as critical to

control formation of the desired form, (b) (4) Provide data to support the choice of these control parameters and the proposed limits.

With regard to the drug substance specification, we note identification tests (i.e., IR spectroscopy and X-ray powder diffraction) are included in the specification to confirm the presence of the desired form, (b) (4) You do not, however, propose limits for other polymorphic forms, or amorphous material in the bulk drug substance. Provide justification for the absence of this control. Additionally, provide supporting data regarding the sensitivity of each method for detection of alternate polymorphic forms or amorphous materials.

Clarify whether drug substance manufactured by the (b) (4), or any batches of the resulting drug product, have been placed on stability. Submit all available stability data.

You have submitted comparative dissolution profiles for the highest strength tablet (400 mg) of drug product manufactured using drug substance obtained from the (b) (4) versus drug product manufactured using drug substance obtained from the (b) (4). Refer to Section 3.2.P.2.2.1, Figure 1. Provide the individual tablet data for review. Additionally, provide comparative dissolution profile data for the lowest tablet strength, 50 mg.

You will need to submit either a formal biowaiver request, with appropriate supporting data, or bioequivalence, data for the lower strengths (i.e., 50 mg, (b) (4), 200 mg, and 300 mg) of the market image tablets. *[Draft comment to be revised in consultation with ONDQA Biopharmaceutics staff]*

**Review, Comments and Recommendation:**

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the dosage form is relatively simple. There are no QbD aspects to the application. Assignment to a single reviewer is recommended. The ONDQA Biopharmaceutics should be consulted regarding the requirements for a bioequivalence study or biowaiver request for the lower strengths of the commercial formulation, and for evaluation of the proposed dissolution test and acceptance criteria.

Martha R. Heimann, Ph.D. \_\_\_\_\_

Pharmaceutical Assessment Lead

\_\_\_\_\_

Date

Ramesh Sood, Ph.D. \_\_\_\_\_

Branch Chief

\_\_\_\_\_

Date

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

**NDA Number: 22-345**

**Applicant: Valeant Pharmaceuticals**

**Stamp Date: 30-Oct-2009**

**Drug Name: retigabine tablets**

**NDA Type: Standard**

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

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

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? \_\_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. **NA**

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22345	ORIG-1	VALEANT PHARMACEUTICA LS NORTH AMERICA	RETIGABINE

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/s/

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MARTHA R HEIMANN  
11/19/2009

RAMESH K SOOD  
11/19/2009