CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

01 May 2013

NDA: **204447/N-000**

Drug Product Name
Proprietary: Brintellix
Non-proprietary: Vortioxetine

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
02 OCT 2012	02 OCT 2012	26 OCT 2012	26 OCT 2012
13 FEB 2013	13 FEB 2013	N/A	N/A

Applicant/Sponsor
Name: Takeda Pharmaceuticals USA, Inc.
Address: One Takeda Parkway
Deerfield, IL 60015
Representative: Joanna Sambor
Telephone: 224-554-2948

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Recommended for approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(1) NDA.

2. SUBMISSION PROVIDES FOR: Marketing authorization.

3. MANUFACTURING SITES:
Takeda Pharmaceutical Company Limited, Osaka Plant
17-85, Jusohonmachi 2-chome
Yodogawa-ku
Osaka 532-8686, Japan

&

H. Lundbeck A/S
Ottiliavej 9
2500 Valby, Denmark

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
- Tablet
- Oral
- 5, 10, 15 and 20 mg per tablet

5. METHOD(S) OF STERILIZATION: The drug product is not sterile.

6. PHARMACOLOGICAL CATEGORY: The drug product is indicated for Major Depressive Disorder.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:
The subject NDA is submitted electronically in the CTD format.

The OND Project Manager forwarded a Microbiology Information Request to the applicant on 14 January 2013. Following is the information request:

> *We acknowledge that the subject drug substance is tested in-house for microbial limits. However, the information in the report, "Analytical Method Validation for LuAA21004 Drug Substance" does not provide adequate verification of the suitability of use of the microbial limit test method with the subject drug substance. Specifically, you did not recover* (b) (4) *after exposure of these organisms to the drug substance. Reference is made to USP<61>, section header Neutralization/Removal of Antimicrobial Activity, which provides a number of microbial limits test procedure modifications for "ensuring the*

validity of the results". Further, USP<61> states that after implementing these procedure modifications, "if no suitable neutralizing method can be found…Then, perform the test with the highest dilution factor compatible with microbial growth and the specific acceptance criterion".

We acknowledge your request to forgo microbial limits testing on the finished drug product. We note that a component of your rationale to forgo this testing is that you will be testing the drug substance in house using the method described in module 3.2.S.4.3. To fully support your rationale to forgo microbial limits testing on the finished drug product, you must adequately verify the suitability of use of the microbial limits tests with the subject drug substance.

- *Amend the NDA with a modified microbial limits test method* (b) (4) *Provide verification study data sets demonstrating the suitability of use of these tests with the subject drug substance.*
- *Amend the NDA to include microbial limits testing at the time zero testing interval of the post approval drug product stability protocol (reference to table 1.h of module 3.2.P.8.2).*

On 13 February 2013, the applicant amended the NDA with a response to this request for information. The responses are summarized and reviewed in appropriate sections of this review.

File Name: N204447R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – NDA 204447/N-000 is recommended for approval from the standpoint of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is manufactured (b) (4)

B. Brief Description of Microbiology Deficiencies – There are no microbiology deficiencies identified.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

D. Contains Potential Precedent Decision(s) ☒No

III. Administrative

A. Reviewer's Signature _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

B. Endorsement Block_____

Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

C. CC Block

N/A

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/s/

JOHN W METCALFE
05/01/2013

STEPHEN E LANGILLE
05/01/2013

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204447 **Applicant:** Takeda Pharmaceuticals, Inc. **Letter Date:** 02 OCT 2012

Drug Name: Vortioxetine **NDA Type:** 505(b)(1); Standard **Stamp Date:** 02 OCT 2012

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?		X	See summary comment below.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Module 3.2.P.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	See summary comment below.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		X	Not applicable to product dosage form.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?		X	See summary comment below.
7	Has the applicant submitted the results of analytical method verification studies?		X	See summary comment below.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			Not applicable.
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?		X	Not applicable to dosage form.
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: The drug product is a tablet. The lack of microbiology information in the NDA identified above does NOT preclude the filing of the NDA since tablets do not present a significant patient risk regarding microbiological quality. The reviewer will decide during the review cycle whether the applicant's proposal to not perform microbial limits release testing is acceptable.

07 November 2012

John W. Metcalfe, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS.

07 November 2012

Stephen E. Langille, Ph.D. Date
Senior Microbiology Reviewer, CDER/OPS/NDMS.

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

/s/

JOHN W METCALFE
11/07/2012

STEPHEN E LANGILLE
11/08/2012