

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205422Orig1s000**

**205422Orig2s000**

**CHEMISTRY REVIEW(S)**

**NDA 205422**  
**Review #1 Addendum**

**Rexulti™ (Brexpiprazole) Tablets**

**Otsuka Pharmaceutical Company, Ltd**

**Wendy I. Wilson-Lee, Ph.D.**

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

**Division of New Drug Quality Assessment I**

**Office of New Drug Quality Assessment**

**Division of Neurology Drug Products**

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

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**Chemistry Review Data Sheet**

1. NDA: 205422
2. REVIEW: #1 Addendum
3. REVIEW DATE: June 2, 2015
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.  
Thomas M. Wong, Ph.D.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Review #1	26-FEB_2015

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment #0025	13 Feb 2015
Amendment #0026	13 Feb 2015

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

Name: Otsuka Pharmaceutical Development &  
Commercialization, Inc.  
Address: 2440 Research Blvd.,  
Rockville, MD 20850  
Representative: Patrick F. Guinn, RAC  
Director, Global Regulatory Affairs  
Telephone: (609) 524-6797

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

- a) Proprietary Name: Rexulti™
- b) Non-Proprietary Name (USAN): Brexpiprazole
- c) Code Name/# (ONDQA only): OPC-34712; OPC-331
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Antidepressant

## 11. DOSAGE FORM: Tablets

## Executive Summary Section

12. STRENGTH/POTENCY: 0.25, 0.5, 1, 2, 3, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name: 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(iH)-one

Mol. Formula: C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S

Mol. Weight: 433.57

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	REVIEW DATE	COMMENTS
(b) (4)	IV		(b) (4)	4	N/A		
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			

<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	101,871 and 103,958	Commercial IND

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	-	-
EES	Acceptable	06/02/2015	Dr. Vipul Dholakia
Pharm/Tox	N/A	-	-
Biopharm	Approval	02/25/2015	Dr. Minerva Hughes
LNC	N/A	-	-
Methods Validation	Acceptable	05/28/2015	Dr. Michael Trehy
DMEPA	N/A	-	-
EA	Acceptable	02/19/2015	Dr. Thomas Wong
Microbiology	Adequate	12/02/2014	Dr. John W Metcalfe

## Chemistry Review for NDA 205422

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

We recommend **approval** of **NDA 205422** for Rexulti™ (Brexpiprazole) Tablets, 0.25, 0.5, 1, 2, 3, and 4 mg packaged in the intended commercial packaging and stored at USP Controlled Room Temperature for up to 36 months.

Please include in the action letter the following comment from the methods validation report from Office of Testing and Research:

Action Letter Comment

The Division of Pharmaceutical Analysis (DPA) suggests the following clarifications to the sample calculations:

Assay for 2, 3 and 4 mg tablets (b) (4)  
Assay for 0.25, 0.5 and 1 mg tablets (b) (4)

1. (b) (4)  
(b) (4) DPA recommends the equations be amended as follows:  
(b) (4) for 0.25 mg tablet  
(b) (4) for 4 mg tablet

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

We approve the Comparability Protocol for Removal of Release Testing for (b) (4) in the Drug Substance.

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

The proposed commercial product is an immediate-release (b) (4) tablets with 6 strengths: 0.25, 0.5, 1, 2, 3, and 4 mg. The tablets are colored, round, shallow convex, bevel edged tablets, debossed with BRX and the tablet strength on one side. The strengths are differentiated by the (b) (4) color and debossing. The trade name for brexpiprazole tablets is Rexulti™. The inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc. Colorants include titanium dioxide, iron oxide and ferrosferric oxide. The tablets will be manufactured in Otsuka Pharmaceutical Company's Tokushima factory located in Japan with two proposed commercial batch size of Batch size-1 and Batch-size-2. Batch size-1 is (b) (4) tablets for 0.25-mg tablets and (b) (4) tablets for 0.5-, 1-, 2-, 3-, 4-mg tablets. Batch size-2 is (b) (4) tablets for 0.25-mg tablets and (b) (4) tablets for 0.5-,

## Executive Summary Section

1-, 2-, 3-, 4-mg tablets. Tablets are packaged in HDPE bottles with 30-count tablets per bottle; (b) (4)

Tablets are stored at 25°C (77°F), excursions permitted between 15 - 30°C (between 59 - 86°F). 24 months of stability data support the proposed shelf life of 36 months when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

### Drug Substance

Brexpiprazole is a serotonergic-noradrenergic-dopaminergic acting compound. It is a small molecule with molecular formula C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S and molecular weight 433.57. (b) (4)

(b) (4). The applicant uses processing parameters within the defined design spaces as process control strategy. The drug substance is manufactured at the Second Tokushima Factory of Otsuka Pharmaceutical Co. Ltd. Located at Tokushima, Japan. The proposed commercial scale is (b) (4) kg. The applicant provided adequate information regarding structure elucidation and confirmation and impurity profile. Available 24 months stability data supports the proposed retest period of (b) (4) months for the drug substance stored below 30°C (b) (4)

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

The tablets are to be administered orally. The recommended dose for major depressive disorder was established at doses of 2 mg/day and 3 mg/day and for treatment of schizophrenia was established at doses of 2 mg/day and 4 mg/day.

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

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. All previously pending issues regarding the dissolution method, facilities evaluation, methods validation evaluation, and evaluation of the need for a control limit for the (b) (4) impurity by the nonclinical reviewer are resolved satisfactorily.

As part of this recommendation, we approve the Comparability Protocol for Removal of Release Testing for (b) (4) in the Drug Substance.

### **D. Risk Assessment**

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation	Risk Evaluation	Lifecycle Considerations/ Comments
Assay/Stability - Drug substance	Degradation under normal or stressed storage conditions.	L	The drug substance is very stable as evident by the registration and stress stability study data.	Acceptable	None.
- Drug product	Sub-potent at the end of product shelf-life	L	The drug product is very stable as evident by the available stability data (b) (4)	Acceptable	None
Content uniformity	Dose to dose variation	L	Processing parameters have been optimized.	Acceptable	None

Executive Summary Section

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation	Risk Evaluation	Lifecycle Considerations/ Comments
Microbial	Micro growth	L	<div style="border: 1px solid red; padding: 5px;">                     (b) (4)                       Blend uniformity studies on the blends of the LTSS show acceptable results with RSD of (b) (4).                       Drug product specification includes microbial limit test.                 </div>	Acceptable	None
Dissolution	Bioavailability of the active	L	BCS Class 2	Acceptable	None

**III. Administrative**

**Wendy I. Wilson - S**  
 Digitally signed by Wendy I. Wilson - S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson - S  
 Date: 2015.06.03 11:31:53 -04'00'

**Olen Stephens - S**  
 Digitally signed by Olen Stephens - S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens - S, 0.9.2342.19200300.100.1.1=2000558826  
 Date: 2015.06.03 11:48:16 -04'00'

NDA #-###

Drug Product Name

**Chemistry Assessment**

At the time of completion of Review #1, the final CMC recommendation for Brexpiprazole Tablets was pending due to the following issues :

- The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspection.
- Awaiting method validation results from Office of Testing and Research.
- Evaluation of the need for a control limit for the (b) (4) impurity by the nonclinical reviewer.

This review covers the final resolution of the pending issues.

(b) (4) Impurity

Impurity	Structure	Origin	Proposed Control Strategy	Maximum Amount Observed in Final Drug Substance (b) (4)

The applicant classified (b) (4). However, the structural alert present in the compound is an (b) (4). The applicant contends that (b) (4) is not observed in the final drug substance. However, data is not provided to support this claim. Information is needed on the amount of (b) (4) in the final drug substance, both in batches supporting clinical and nonclinical studies to evaluate the potential impact on patient safety. We requested data on the amount of (b) (4) in the final drug substance batches used to support Phase III clinical and pivotal nonclinical studies. The applicant committed to re-evaluating the data in the December 2014 response to our request and also committed to submitting the re-evaluation to the agency by the end of March 2015.

The applicant provided data on the amount of (b) (4) the requested data from clinical, nonclinical, and stability batches. The reported amount of OPC was < (b) (4)% for all drug substance batches, well below the reporting threshold. For the drug product, the reported amounts was (b) (4)% - (b) (4) at release and (b) (4)% - (b) (4)% on stability, below the identification threshold. In addition, the applicant provided in-silico analysis results in line with ICH M7. Pharm/tox confirmed on 19-MAR-2015 that based on the QSAR assessment, (b) (4) is not predicted to be mutagenic and that no additional controls for this impurity/degradant are needed.

**Evaluation: Adequate** – Based on the information provided and the recommendation from the pharm/tox review team, no additional controls are required for (b) (4).

Methods Validation Report (OTR)

The Division of Pharmaceutical Analysis (DPA) completed their evaluation of the methods validation information and found the evaluated analytical procedures acceptable for quality control and regulatory purposes (Methods Validation Report dated May 28, 2015). DPA recommended clarifications to the sample calculations for assay and requests the following comment be sent to the applicant:

NDA #-###

Drug Product Name

The Division of Pharmaceutical Analysis (DPA) suggests the following clarifications to the sample calculations:

Assay for 2, 3 and 4 mg tablets (b) (4)  
Assay for 0.25, 0.5 and 1 mg tablets (b) (4)

1. (b) (4) DPA recommends the equations be amended as follows:

(b) (4) for 0.25 mg tablet  
(b) (4) for 4 mg tablet

**Evaluation: Adequate** – The evaluated analytical procedures are acceptable for quality control and regulatory purposes.

### Facilities Evaluation

The Division of Facilities Assessment in the Office of Process and Facilities found that all facilities associated with the commercial manufacture and testing of brexpiprazole tablets are acceptable.

The screenshot shows a web-based form titled "Overall Manufacturing Inspection Recommendation" for NDA 205422-Orig1-New/NDA(1). The form is currently in the "Inspection Management Form" view. It lists several facilities with their names, addresses, and approval dates. The "Overall Manufacturing Inspection Recommendation" section is set to "Approve".

Facility Name	Address	Approval Date
(b) (4)	(b) (4)	(b) (4)
CTL CONTROL TESTING LABORATORY		2015-08-23
OTSUKA PHARMACEUTICAL CO., LTD.	3003808559   CSN NON-STERILE API BY CHEMICAL SYNTHESIS	2015-09-30
(b) (4) CTL CONTROL TESTING LABORATORY		2016-06-27
OTSUKA PHARMACEUTICAL CO LTD	3002809299   TCM TABLETS, PROMPT RELEASE	2016-09-18
OTSUKA PHARMACEUTICAL CO., LTD. - SECOND TOKUSHIMA FACTORY	3002807834   CSN NON-STERILE API BY CHEMICAL SYNTHESIS	2017-06-26
(b) (4)		(b) (4)

**Overall Manufacturing Inspection Recommendation**

Approve  
 Withhold

Overall Application Re-evaluation Date: 8/16/15

Save Cancel

**Evaluation: Adequate** – The overall manufacturing inspection recommendation is approve.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION REPORT SUMMARY**

**TO:** Wendy Wilson and Thomas Wong, CMC Reviewer

Office of New Drug Quality Assessment (ONDQA)

E-mail Address: wendy.wilson@fda.hhs.gov and Thomas.wong@fda.hhs.gov

Phone: (301)-796-1651 (Wendy) and (301)-796-1608 (Thomas)

Fax: (301)-796-9747

**FROM:** FDA

Division of Pharmaceutical Analysis

Michael Trehy, MVP Coordinator

645 S Newstead Avenue

St. Louis, MO 63110

Phone: (314) 539-3815

**Through:** David Keire, Acting Lab Chief, Branch I

Phone: (314) 539-3850

**SUBJECT:** Methods Validation Report Summary

---

Application Number: 205422

Name of Product: Brexpiprazole tablets, 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg

Applicant: Otsuka Pharmaceutical Company, Ltd Applicant's Contact Person: David Goldberger

Address: 1 University Square Drive, Suite 500, Princeton, NJ

Telephone: 609-524-6797 Fax: 609-955-3368

---

Date Methods Validation Consult Request Form Received by DPA: 10/31/2014

Date Methods Validation Package Received by DPA: 10/31/2014

Date Samples Received by DPA: 12/4/2014

Date Analytical Completed by DPA: 5/27/2014

---

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes.

**2.** Methods are acceptable with modifications (as stated in accompanying report).

**3.** Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



Date: May 27, 2015

To: Wendy Wilson, CMC Reviewer, ONDQA  
Thomas Wong, CMC Reviewer, ONDQA  
David Claffey, CMC Lead, ONDQA

Through: David Keire, Ph. D., Deputy Director, Division of Pharmaceutical Analysis

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 205422  
Brexpiprazole tablets, 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg  
Otsuka Pharmaceutical Company, Ltd.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Drug-related impurities by HPLC (b) (4)
- Assay by HPLC (b) (4)
- (b) (4)
- Assay for 2, 3, 4 mg tablets (b) (4)
- Assay for 0.25, 0.5 and 1 mg tablets (b) (4)
- Impurities/degradation products, drug product (b) (4)
- Dissolution, 0.25 mg tablets (b) (4)

The Division of Pharmaceutical Analysis (DPA) suggests the following clarifications to the sample calculations:

Assay for 2, 3 and 4 mg tablets (b) (4)

Assay for 0.25, 0.5 and 1 mg tablets (b) (4)

1. (b) (4)

DPA recommends the equations be amended as follows:

(b) (4) or 0.25 mg tablet  
for 4 mg tablet

Link to analyst's worksheets: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880a422c5>

**Drug-related impurities by HPLC** (b) (4)

Specifications: (b) (4)

**Assay by HPLC** (b) (4)

Specification: (b) (4)

	%Content	Avg %Content	RRT	%impurity	Specifications	Result
<b>Assay</b>	(b) (4)					<b>Pass</b>
<b>Impurities</b>	(b) (4)				(b) (4)	
<b>Total impurities</b>						

(b) (4)

Specification: (b) (4)

Result: (b) (4) (Pass)

**Assay for 4 mg tablets** (b) (4)

**Assay for 0.25 mg tablets** (b) (4)

Specification: (b) (4)

Dosage	Amount (mg)	%Label Claim	Specification	Assay Result
0.25 mg tablet	(b) (4)			<b>Pass</b>
4 mg tablet				

**Impurities/degradation products, drug product** (b) (4)

Specifications: (b) (4)

Component	RT	RRT	0.25mg tablet %Impurity Avg(2)	4mg tablet %Impurity Avg(2)	Specification	Result
(b) (4)						<b>Pass</b>

**Dissolution by HPLC** (b) (4)

Specification: (b) (4)

%Dissolved

Time, min.	Low%(6 )	High%(6 )	Avg.(6)	SD	%RSD (b) (4)	Result
10	(b) (4)					<b>Pass</b>
20						
<b>30</b>						
45						
60						

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

/s/  
-----

MICHAEL L TREHY  
05/28/2015

DAVID A KEIRE  
05/28/2015

**NDA 205-422****Rexulti™ (Brexpiprazole) Tablets****Otsuka Pharmaceutical Company, Ltd****Wendy I. Wilson-Lee, Ph.D.****Thomas M. Wong, Ph.D.****Division of New Drug Quality Assessment I****Office of New Drug Quality Assessment****Division of Neurology Drug Products****Review of Chemistry, Manufacturing, and Controls**

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**Chemistry Review Data Sheet**

1. NDA: 205422
2. REVIEW: #1
3. REVIEW DATE: Feb 26, 2015
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.  
Thomas M. Wong, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

IND 101,871 and IND 103,958

Document Date

Commercial IND

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original submission  
Amendment #0002  
Amendment #0009  
Amendment #0015  
Amendment #0019  
Amendment #0021  
Amendment #0023  
Amendment #0024  
Amendment #0025

Document Date

11 Jul 2014  
5 Aug 2014  
14 Oct 2014  
24 Dec 2014  
31 Jan 2015  
1 Feb 2015  
18 Feb 2015  
13 Feb 2015  
13 Feb 2015

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

Name: Otsuka Pharmaceutical Development &  
Commercialization, Inc.  
Address: 2440 Research Blvd.,  
Rockville, MD 20850  
Representative: Patrick F. Guinn, RAC  
(See Amendment #0024 dated  
2/13/2015) Director, Global Regulatory Affairs  
Telephone: (609) 524-6797

## Executive Summary Section

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

- a) Proprietary Name: Rexulti™
- b) Non-Proprietary Name (USAN): Brexpiprazole
- c) Code Name/# (ONDQA only): OPC-34712; OPC-331
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 1
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Antidepressant

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: 0.25, 0.5, 1, 2, 3, and 4 mg

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name: 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(iH)-one

Mol. Formula: C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S

Mol. Weight: 433.57

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

## Executive Summary Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4			
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				
	III		4				

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

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Other codes indicate why the DMF was not reviewed, as follows:

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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	101,871 and 103,958	Commercial IND

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

## Executive Summary Section

Biometrics	NA		
EES			
Pharm/Tox	N/A		
Biopharm	Approval	02/25/2015	Dr. Minerva Hughes
LNC	N/A		
Methods Validation			
DMEPA	N/A		
EA	Acceptable	02/19/2015	Dr. Thomas Wong
Microbiology	Adequate	12/02/2014	Dr. John W Metcalfe

## Chemistry Review for NDA 205422

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

The final CMC recommendation on the NDA 205422 for Rexulti™ (Brexpiprazole) Tablets, 0.25, 0.5, 1, 2, 3, and 4 mg will depend on the resolution of the following issues :

- The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspection.
- Awaiting method validation results from Office of Testing and Research.
- Evaluation of the need for a control limit for the (b) (4) impurity by the nonclinical reviewer.

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

(b) (4)

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

The proposed commercial product is an immediate-release (b) (4) tablets with 6 strengths: 0.25, 0.5, 1, 2, 3, and 4 mg. The tablets are colored, round, shallow convex, bevel edged tablets, debossed with BRX and the tablet strength on one side. The strengths are differentiated by the (b) (4) color and debossing. The trade name for brexpiprazole tablets is Rexulti™. The inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc. Colorants include titanium dioxide, iron oxide and ferrous ferric oxide. The tablets will be manufactured in Otsuka Pharmaceutical Company's Tokushima factory located in Japan with two proposed commercial batch size of Batch size-1 and Batch-size-2. Batch size-1 is (b) (4) tablets for 0.25-mg tablets and (b) (4) tablets for 0.5-, 1-, 2-, 3-, 4-mg tablets. Batch size-2 is (b) (4) tablets for 0.25-mg tablets and (b) (4) tablets for 0.5-, 1-, 2-, 3-, 4-mg tablets. Tablets are packaged in HDPE bottles with 30-count tablets per bottle;

Tablets are stored at 25°C (77°F), excursions permitted between 15 - 30°C (between 59 - 86°F). 24 months of stability data support the proposed shelf life of 36 months when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

**Drug Substance**

Brexpiprazole is a serotonergic-noradrenergic-dopaminergic acting compound. It is a small molecule with molecular formula C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S and molecular weight 433.57. (b) (4)

(b) (4)

Executive Summary Section

(b) (4)

(b) (4). The applicant uses processing parameters within the defined design spaces as process control strategy. The drug substance is manufactured at the Second Tokushima Factory of Otsuka Pharmaceutical Co. Ltd. Located at Tokushima, Japan. The proposed commercial scale is kg (b) (4). The applicant provided adequate information regarding structure elucidation and confirmation and impurity profile. Available 24 months stability data supports the proposed retest period of (b) (4) months for the drug substance stored below 30°C (b) (4).

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

The tablets are to be administered orally. The recommended dose for major depressive disorder was established at doses of 2 mg/day and 3 mg/day and for treatment of schizophrenia was established at doses of 2 mg/day and 4 mg/day.

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

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC perspective NDA 205422 for Rexulti™ (Brexipiprazole) Tablets can be approved pending the biopharmaceutics reviewer's acceptance on the dissolution specification, evaluation of the need for control of the (b) (4) impurity, and acceptable recommendation from Office of Compliance.

**D. Risk Assessment**

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation	Risk Evaluation	Lifecycle Considerations / Comments
Assay/Stability - Drug substance  - Drug product	Degradation under normal or stressed storage conditions. Sub-potent at the end of product shelf-life	L	The drug substance is very stable as evident by the registration and stress stability study data.	Acceptable	None.
		L	The drug product is very stable as evident by the available stability data (b) (4) Processing parameters have been optimized. (b) (4)	Acceptable	None
Content uniformity	Dose to dose variation	L	(b) (4) Blend uniformity studies on the blends of the LTSS show acceptable results with RSD of (b) (4)	Acceptable	None

Executive Summary Section

Microbial	Micro growth	L	Drug product specification includes microbial limit test.	Acceptable	None
Dissolution	Bioavailability of the active	L	BCS Class 2	Acceptable	None

**III. Administrative**

**A. Reviewer's Signature**

Thomas M. Wong -A  
Digitally signed by Thomas M. Wong -A  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Thomas M. Wong -A,  
 0.9.2342.19200300.100.1.1=1300437649  
 Date: 2015.02.26 13:23:43 -05'00'

Wendy I. Wilson -S  
Digitally signed by Wendy I. Wilson -S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S  
 Date: 2015.02.26 13:10:12 -05'00'

**B. Endorsement Block**

Olen Stephens -S  
Digitally signed by Olen Stephens -S  
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S,  
 0.9.2342.19200300.100.1.1=2000558826  
 Date: 2015.02.26 13:27:47 -05'00'

**C. CC Block**

NDA #-###

Drug Product Name

## Chemistry Assessment

## I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3:

## S DRUG SUBSTANCE [Brexpiprazole, Otsuka Pharmaceutical Co. Ltd.]

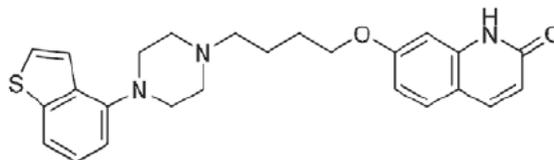
## S.1 General Information

## S.1.1 Nomenclature

**Chemical Name:** 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(iH)-one  
**Generic name (USAN):** Brexpiprazole  
**Common name:** Brexpiprazole  
**Trade name:** Not provided  
**INN:** Brexpiprazole  
**CAS No.:** 913611-97-9  
**Code No.:** OPC-34712; OPC-331

## S.1.2 Structure

**Molecular formula:** C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S  
**Molecular weight:** 433.57



## S.1.3 General Properties

<b>Description</b>	White to off-white crystals or crystalline powder
<b>Optical Rotation</b>	Not optically active
<b>Hygroscopicity</b>	(b) (4)
<b>Solubility</b>	
<b>pH</b>	
<b>pKa</b>	
<b>Partition Coefficient</b>	
<b>Melting Point</b>	

## S.2 Manufacture

## S.2.1 Manufacturers

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**S.5 Reference Standards or Materials**

Lot S12G74 is the primary brexpiprazole reference standard. The primary reference standard was prepared from brexpiprazole final drug substance, undergoing additional purification steps. The reference standard specification includes the following test attributes: description (visual), identification (UV, IR, proton NMR, MS), melting point, drug-related impurities, residual solvent (b) (4), residue on ignition, assigned purity (mass balance method).

**Evaluation: Adequate** – The proposed batch is suitable for use as the reference standard batch. Analytical procedures were provided for the reference standard when different from proposed regulatory drug substance analytical procedures. Analytical results for primary reference standard and previous two reference standard batches were also provided.

**S.6 Container Closure System**

Component	Function	Contact Surface	Material	Supplier	Regulatory Status
(b) (4)	Primary Container	Yes	(b) (4)	(b) (4)	21 CFR 177.1520
	Secondary Container	No			21 CFR 177.1520

(b) (4)

**Evaluation: Adequate** – The proposed commercial container closure is typical for drug substance. The registration stability data supports the use of the proposed container closure. Additional information on the tertiary and shipping containers is not required for approval as they do not contact the drug substance. The drug substance contact surface complies with regulatory requirements. The applicant qualified the (b) (4) description, IR spectrum, and extractable substances (b) (4)

NDA #-###

Drug Product Name

**S.7 Stability****S.7.1 Stability Summary and Conclusions (copied from submission)**

<b>Table 3.2.S.7.3.2-1 Information on Brexpiprazole Batches Placed on Stability: Second Tokushima Factory</b>			
<b>Drug Substance Lot Number</b>	<b>C10H92M</b>	<b>C10H95M</b>	<b>C10H00M</b>
Site of manufacture	Second Tokushima Factory		
Approximate batch size	(b) (4)		
Date of manufacture	23 Aug 2010	26 Aug 2010	31 Aug 2010
Pilot/ Production scale	Pilot scale		
Test	Date stability started		
Long term testing: (b) (4) (b) (4)	24 Nov 2010	24 Nov 2010	24 Nov 2010
Accelerated testing: (b) (4) (b) (4)	29 Nov 2010	29 Nov 2010	29 Nov 2010
Stress testing (b) (4) (b) (4)	01 Nov 2010	-	-
Stress testing (b) (4) (b) (4)	01 Nov 2010	-	-
Stress testing (b) (4) (b) (4)	01 Nov 2010	-	-
Photostability: (b) (4) (b) (4)	01 Nov 2010	-	-
Data presented (month)	24	24	24
Specification failures	No	No	No
Site of analysis	Second Tokushima Factory		

- = No test is scheduled

<b>Table 3.2.S.7.3.2-2 Information on Brexpiprazole Batches Placed on Stability: Saga Factory</b>			
<b>Drug Substance Lot Number</b>	<b>CS12I87M1</b>	<b>CS12I88M1</b>	<b>CS12I89M1</b>
Site of manufacture	Saga Factory		
Approximate batch size	(b) (4)		
Date of manufacture	18 Sep 2012	19 Sep 2012	20 Sep 2012
Pilot/ Production scale	Pilot scale		
Test	Date stability started		
Long term testing: (b) (4) (b) (4)	23 Oct 2012	23 Oct 2012	23 Oct 2012
Accelerated testing: (b) (4) (b) (4)	23 Oct 2012	23 Oct 2012	23 Oct 2012
Data presented (month)	9	9	9
Specification failures	No	No	No
Site of analysis	Saga Factory		

**Stability Tests and Analytical Procedures:** Description (visual), Identification (IR), Melting Point, Drug-Related Impurities (HPLC), Residual Solvents (GC), (b) (4) Assay (HPLC), Particle Size distribution (Laser diffraction); Same acceptance criteria and analytical procedures used at release used for stability testing

(b) (4)

NDA #-###

Drug Product Name

**S.7.2** *Post-approval Stability Protocol and Stability Commitment*

(b) (4)

**Evaluation: Adequate.****S.7.3** *Stability Data**Summary of Registration Stability Data*

NDA #-###

Drug Product Name

Test	Method	Acceptance Criteria		Typical Ranges Observed		
			<b>Long-Term Conditions</b> <small>(b) (4)</small>		<b>Accelerated Conditions</b> <small>(b) (4)</small>	
			<b>Second Tokushima Factory (up to 24 Months)</b>	<b>Saga Factory (up to 9 Months)</b>	<b>Second Tokushima Factory (6 Months)</b>	<b>Saga Factory (6 Months)</b>
<b>Description</b>	Visual G01-331-BUL-007	<small>(b) (4)</small>				
<b>Identification</b>	<small>(b) (4)</small>		Comparable to that of reference standard	Comparable to that of reference standard	Comparable to that of reference standard	Comparable to that of reference standard
	<small>(b) (4)</small>		Comparable to that of reference standard	Comparable to that of reference standard	Comparable to that of reference standard	Comparable to that of reference standard
<b>Melting Point</b>	<small>(b) (4)</small>					
<b>Drug Related Impurities</b>						<small>(b) (4)</small>

NDA #-###

Drug Product Name

Test	Method	Acceptance Criteria		Typical Ranges Observed		
(b) (4)						
<b>Assay</b>	(b) (4)					
<b>Particle size distribution</b>	(b) (4)					

**Evaluation: Adequate** – Photostability studies were conducted on drug substance following ICH Q1B Option 2 guidelines. The results indicate that drug substance is not light sensitive. The proposed storage condition does not include special storage instructions. The recommend storage is “Up to 30°C.” The proposed retest is  $\frac{(b)(4)}{4}$  years. The stability data supports the proposed re-test period.

## P DRUG PRODUCT

### P.1 Description and Composition of the Drug Product

The proposed commercial product is an immediate-release (b) (4) tablets with 6 strengths: 0.25, 0.5, 1, 2, 3, and 4 mg. The tablets are colored, round, shallow convex, bevel edged tablets, debossed with BRX and the tablet strength on one side. The strengths are differentiated by (b) (4) color and debossing. Below is the composition of the (b) (4) tables:

NDA #-###

Drug Product Name

Component	Quality Standard	Function	0.25-mg		0.5-mg		1-mg		2-mg		3-mg		4-mg	
			mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)
Brexpiprazole	In-house	Active ingredient	0.25		0.5		1.0		2.0		3.0		4.0	
Lactose monohydrate <sup>b</sup>	NF													
Com starch	NF													
Microcrystalline cellulose	NF													
Low-substituted hydroxypropyl cellulose	NF													
Hydroxypropyl cellulose <sup>c</sup>	NF													
Magnesium stearate <sup>d</sup>	NF													
Total tablet weight (mg)			93.0		93.0		93.0		93.0		93.0		93.0	
Tablet description (Tablet weight / diameter : 93 mg / 6 mm)			Light brown, round, shallow convex, beveled-edged tablet, debossed with BRX and 0.25 on one side		Light orange, round, shallow convex, beveled-edged tablet, debossed with BRX and 0.5 on one side		Light yellow, round, shallow convex, beveled-edged tablet, debossed with BRX and 1 on one side		Light green, round, shallow convex, beveled-edged tablet, debossed with BRX and 2 on one side		Light purple, round, shallow convex, beveled-edged tablet, debossed with BRX and 3 on one side		White, round, shallow convex, beveled-edged tablet, debossed with BRX and 4 on one side	

NF = National Formulary; USP = US Pharmacopeia; qs = quantity sufficient;



**Evaluation:** Adequate. The applicant provided sufficient information on the composition of the proposed commercial tablets. All excipients are within the range as listed in the FDA approved drug inactive ingredients. The excipients are commonly used in solid dosage forms. The drug load in all strengths core tablets is low.

## P.2 Pharmaceutical Development

### P.2.1 Components of the Drug Product

NDA #-###

Drug Product Name

P.2.1.1 Drug Substance

**Comment:** There is a particle size control in the drug substance specification. In the original submission, it was proposed that the mean particle size is (b) (4) and (b) (4) of the particles: (b) (4). Upon request, the applicant revised the proposed particle size distribution (Amendment #0015) (b) (4) (see drug substance specification). The dissolution results of the registration batches showed more than (b) (4) of brexpipazole dissolved in 30 minutes.

Compatibility with excipients:

In the compatibility with excipients study, physical mixtures of drug substance and each excipient were described in the following results summary table. The mixtures were stored (b) (4) (b) (4) for 4 weeks, and then assessed using HPLC.

#### P.2.1.2 Excipients

The applicant mentioned that lactose monohydrate (b) (4) and (b) (4) Magnesium stearate (b) (4).

**Comment:** All the excipients are commonly used for tablet formulation and are USP/NF compendial materials (b) (4). The components (b) (4) used in the (b) (4) tablets are all compendial materials and is provided the compendial references in Module 3.2.P.4.2 - Control of Excipients of the NDA.

#### P.2.2 Drug Product

##### P.2.2.1 Formulation Development

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### P.2.3 Manufacturing Process Development

The applicant mentioned that the manufacturing method for the drug product remained the same since phase 1 trials except the increase in batch size and (b) (4)

(b) (4) A summary of factors (b) (4) that potentially affecting CQA is provided in the following table.

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#### P.2.4 Container Closure System

The product will be packaged in 60 cc high density polyethylene (HDPE) bottles in 30-count

(b) (4)



(b) (4)

**Final Evaluation: Adequate.** The response is acceptable.

#### P.2.5 Microbiological Attributes

NDA #-###

Drug Product Name

The applicant mentioned that all batches manufactured to date showed very low microbial count, yeast and mold count, and absence of Escherichia Coli. The manufacturing facilities comply with GMP requirements that included equipment cleaning and appropriate environmental monitoring for microbial contamination.

**Evaluation:** Acceptable. The batch analysis data on 18 registration batches showed low microbial count. See section P.5.1 – Specification for discussion.

**P.2.6 Compatibility**

The applicant stated that this section is not applicable for tablets.

**Evaluation:** Acceptable.

**P.3 Manufacture**

**P.3.1 Manufacturers**

Manufacture	Responsibility
Tokushima Factory Otsuka Pharmaceutical Co., Ltd. 463-10, Kagasuno, Kawauchi-cho Tokushima-shi, Tokushima 771-0192 Japan Facility Establishment Identifier: 3002809299  Note - Tokushima Factory was inspected for general GMP in July - August 2012.	<ul style="list-style-type: none"> <li>• Manufacture of (b) (4) brexpiprazole tablets</li> <li>• Analytical testing of the (b) (4) brexpiprazole tablets</li> </ul>



(b) (4)

**Evaluation:** Adequate. At the time of this review, the Office of Compliance has not yet provided an overall acceptable recommendation for the manufacturing sites.

**P.3.2 Batch Formula**

NDA #-###

Drug Product Name

Brexpiprazole tablets are manufactured (b) (4). The applicant stated that to provide a flexible manufacturing to address market demands for 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets, a single batch (b) (4) may compose one lot of tablets (batch size-1) or two consecutive batches (b) (4) may be one lot (batch size-2). (b) (4)

The manufacturing processes and equipment used are the same for both approaches.

### Batch size-1

Component	Specification	0.25-mg Tablets (kg/Batch)	0.5-mg Tablets (kg/Batch)	1-mg Tablets (kg/Batch)	2-mg Tablets (kg/Batch)	3-mg Tablets (kg/Batch)	4-mg Tablets (kg/Batch)
Brexpiprazole	In-house	(b) (4)					
Lactose monohydrate	NF						
Corn starch	NF						
Microcrystalline cellulose	NF						
Low-substituted hydroxypropyl cellulose	NF						
Hydroxypropyl cellulose	NF						
Magnesium stearate	NF						
	(b) (4)						
<b>Total tablet weight (kg)</b>		(b) (4)	93.0	93.0	93.0	93.0	93.0

### Batch size-2

Component	Specification	0.25-mg Tablets (kg/Batch)	0.5-mg Tablets (kg/Batch)	1-mg Tablets (kg/Batch)	2-mg Tablets (kg/Batch)	3-mg Tablets (kg/Batch)	4-mg Tablets (kg/Batch)
Brexpiprazole	In-house	(b) (4)					
Lactose monohydrate	NF						
Corn starch	NF						
Microcrystalline cellulose	NF						
Low-substituted hydroxypropyl cellulose	NF						
Hydroxypropyl cellulose	NF						
Magnesium stearate	NF						
	(b) (4)						
<b>Total tablet weight (kg)</b>		(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

NF = National Formulary; USP = US Pharmacopoeia; cc = quantity coefficient

**Evaluation:** Adequate. There are two proposed commercial batch sizes. The applicant provided sufficient information on the batch formula of these batch sizes.

	Batch size (tablets)					
Tablet strength	0.25 mg	0.5-mg	1-mg	2-mg	3-mg	4-mg
Batch size-1	(b) (4)					
Batch size-2						

NDA #-###

Drug Product Name

**P.3.4 Controls of Critical Steps and Intermediates**

The applicant stated that based on risk assessment, mitigation of risk factors and manufacturing development studies, there are no critical steps in the entire manufacturing process.

**Evaluation:** The reviewer is in agreement with the applicant's evaluation.

**P.3.5 Process Validation and/or Evaluation**

The applicant manufactured three different batches of each of the 6 strength tablets as the registration batches as well as justification study batches. The batch sizes of these batches were the proposed larger batch size, i.e. Batch size-2. During the justification study, the following were studied:

- [redacted] (b) (4)
- blending uniformity [redacted] (b) (4)
- tablets properties were evaluated [redacted] (b) (4)
- tablets properties [redacted] (b) (4).

**Evaluation:** Adequate. All results of the studied items were well within specifications. The applicant mentioned that the manufacturing of 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets (for batch size-1 and -2), and also the packaging processes for brexpiprazole tablets will be validated prior to launch.

**P.4 Control of Excipients****P.4.1 Specifications**

All excipients used to manufacture brexpiprazole tablets are compendial excipients [redacted] (b) (4). The components [redacted] (b) (4) are compendial ingredients.

[redacted] (b) (4)

NDA #-###

Drug Product Name

When received from an established supplier, the excipients are either fully tested or subjected to identification testing and accepted on the basis of the suppliers' Certificate of Analysis. Magnesium stearate (b) (4). Lactose monohydrate is (b) (4). The BSE certificate for lactose is provided.

**Initial Evaluation:** Inadequate. There was no specification established (b) (4). The applicant will be requested to provide the specification.

The following comment was sent to the applicant on 12/4/14:

Provide a copy of the specification with test method (b) (4).

The applicant provided the specification with test method on 12/24/14 via Amendment # 0015.

**Final Evaluation:** Adequate. The proposed specification (b) (4) is acceptable.

#### P.4.2 Excipients (b) (4)

Magnesium stearate (b) (4). Lactose monohydrate (b) (4)

**Evaluation:** The applicant included in the submission a copy of declaration/certificate of suitability from (b) (4) supplier of the lactose monohydrate, that their products meet the guideline EMA/410/01.

#### P.4.3 Novel Excipients

The formulation of brexpiprazole tablets does not include any novel excipients.

**Evaluation:** All excipients used are commonly used in solid dosage forms.

### P.5 Control of Drug Product

#### P.5.1 Specification(s)

All strengths of brexpiprazole tablets have been assigned the same specification.

Below is the revised drug product specification (Amendment #0015 dated 12/24/14). (b) (4)

(b) (4) Upon the request of the microbiology reviewer, the applicant agreed to test at the release of each batch. The revised specification was submitted to reflect the agreement (Amendment #0009 dated 10/14/14).

NDA #-###

Drug Product Name

Test Item	Specifications	Test Method
Description/Appearance	Conforms to Note	Visual
Identification (HPLC: (b) (4))	Retention time and spectrum comparable to the reference standard	HPLC method with (b) (4)
Impurities/Degradation products	(b) (4)	HPLC
Uniformity of dosage units Content uniformity <sup>a</sup>	Conforms to USP	HPLC
Dissolution	Q = (b) (4) in 30 minutes	USP, Apparatus 2, 50 rpm, 900 mL of 0.05 mol/L acetate buffer
Assay	(b) (4) of the label claim	HPLC
Microbial limit test		
Microbial enumeration tests	TAMC: (b) (4) cfu/g, TYMC: (b) (4) cfu/g	USP <61>, Pour-plate method
Tests for specified microorganisms	<i>E. coli</i> : Absent	USP <62>

Note: 0.25-mg tablets: light brown round film coated tablets, debossed with "BRX" and "0.25" on one side; 0.5-mg tablets: light orange round film coated tablets, debossed with "BRX " and "0.5" on one side; 1-mg tablets: light yellow round film coated tablets, debossed with "BRX " and "1" on one side; 2-mg tablets: light green round film coated tablets, debossed with "BRX " and "2" on one side; 3-mg tablets: light purple round film coated tablet, debossed with "BRX" and "3" on one side; 4-mg tablets: white to off-white round film coated tablet, debossed with "BRX" and "4" on one side

(b) (4) TAMC = total aerobic microbial count; TYMC = total combined yeasts and moulds count

<sup>a</sup> performed only at release



(b) (4)

**The following comment was sent to the applicant on 12/4/14:**

Add a second ID method, such as HPLC with retention time of the sample corresponds to the reference standard, in accordance to the ICH Q6A.

The applicant responded to the request on 12/24/14 via Amendment # 0015 that they agreed to add a second ID method, such as HPLC with retention time of the sample corresponds to the reference standard, in accordance to the ICH Q6A. The revised specification reflects the change is shown above.

NDA #-###

Drug Product Name

**Second Evaluation:** Adequate **pending** on the acceptance of the dissolution by the biopharmaceutics reviewer. The response to the addition of a second ID method is acceptable.

**P.5.2 Analytical Procedures**

The applicant provided the following analytical procedure summary for the (b) (4) tablets:

Test Item	Tablet Strength	Method Number
Description/Appearance	0.25-, 0.5-, 1-, 2-, 3-, and 4-mg	(b) (4)
Identification (HPLC- (b) (4))	0.25-, 0.5-, and 1-mg	
	2-, 3-, and 4-mg	
Impurities/Degradation products	0.25-, 0.5-, 1-, 2-, 3-, and 4-mg	
Uniformity of dosage units	0.25- and 0.5-mg	
	1-, 2-, 3-, and 4-mg	
Dissolution	0.25- and 0.5-mg	
	1- and 2-mg	
	3- and 4-mg	
Assay	0.25-, 0.5-, and 1-mg	
	2-, 3-, and 4-mg	
Microbial limit test	0.25-, 0.5-, 1-, 2-, 3-, and 4-mg	
Microbial enumeration tests		
Tests for specified microorganisms ( <i>Escherichia coli</i> )		



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NDA #-###

Drug Product Name



(b) (4)

**Final Evaluation:** Adequate. The response is acceptable. All HPLC methods have been updated

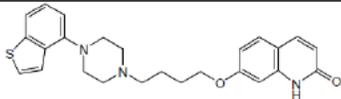
(b) (4)

**P.5.3 Validation of Analytical Procedures**

The applicant performed validations on the test methods for impurities/degradation, assay and dissolution of the (b) (4) tablets. Below are the summary of the results:

**Validation summary for the HPLC method for the quantification of impurities/degradation products in the (b) (4) tablets:**

The studies included specificity, linearity, detection limit, relative response, accuracy (recovery), quantitation limit, precision (repeatability and intermediate precision), range, and robustness.

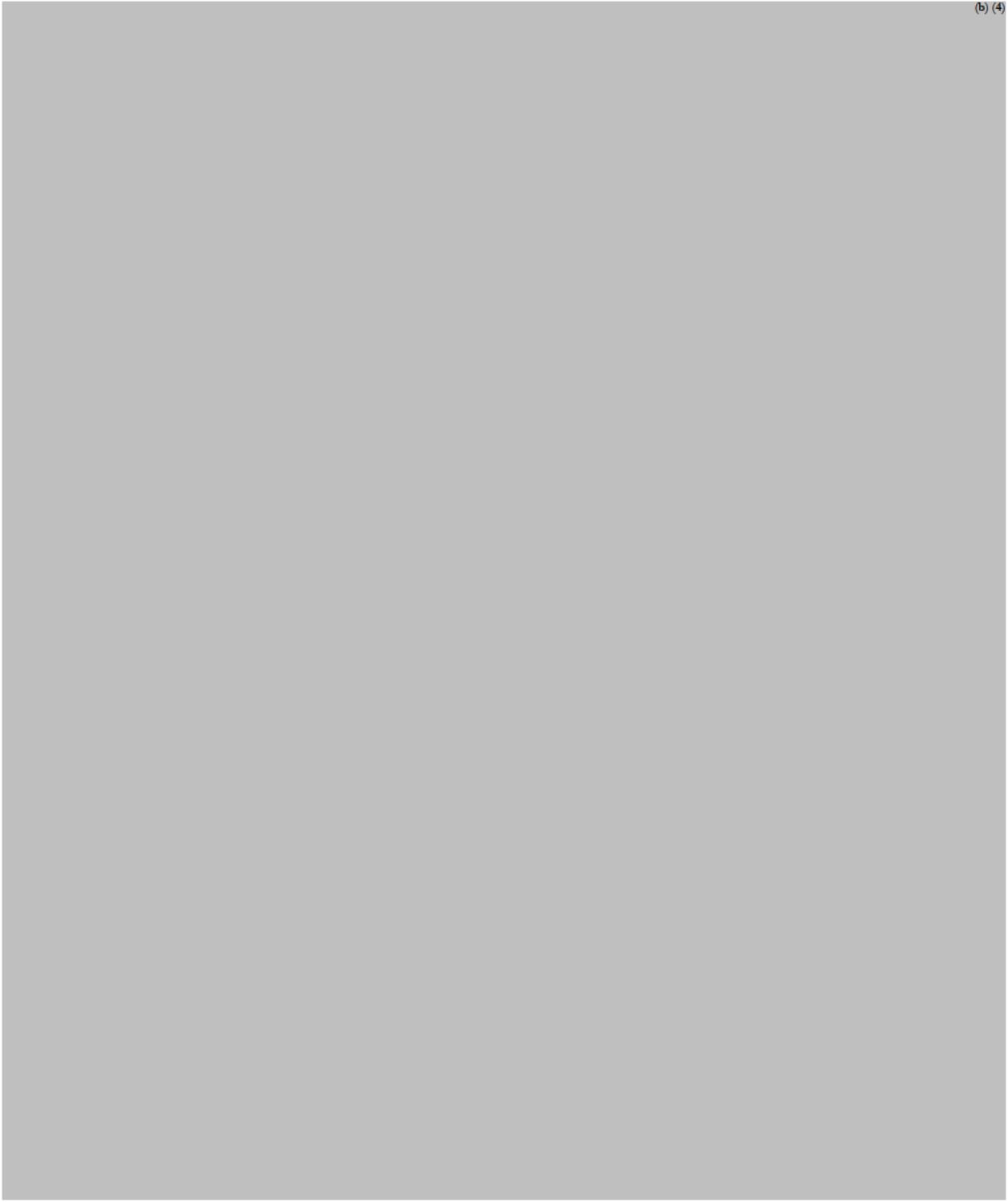
Compound	Structural Formula
Brexpiprazole	

(b) (4)



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(b) (4)



**Validation summary for the HPLC method for assay for brexpiprazole content in the (b) (4) tablets:**

(b) (4)

NDA #-###

Drug Product Name

The studies included specificity, linearity, accuracy (recovery), precision (repeatability and intermediate precision), range, robustness, and stability of solution.

<b>Item</b>	<b>Result</b>
Specificity	(b) (4)
Linearity	
Accuracy	
Precision	
Repeatability	
Intermediate precision	
Range	
Robustness	
HPLC condition	
Stability of solution	

NDA #-###

Drug Product Name

**Validation summary for the HPLC and UV methods for dissolution test for** (b) (4)  
**tablets:**

The studies included specificity, linearity, accuracy (recovery), precision (repeatability and intermediate precision), range, robustness, and stability of solution.

Specificity	(b) (4)
Linearity	
Accuracy (recovery)	
Precision	
Repeatability	

NDA #-###

Drug Product Name

(b) (4)

Intermediate precision	
Range	
Robustness	
Testing condition of HPLC	

NDA #-###

Drug Product Name

	(b) (4)
PH of dissolution medium	
Stability of solution	
Effect of degassing of dissolution medium	

**EVALUATION:** Adequate. The analytical procedure methods have been shown to be specific, linear, accurate, precise and sensitive over the ranges presented. All results were within acceptance criteria.

**P.5.4 Batch Analyses**

The applicant provided batch analysis data on the following registration batches. These batches were manufactured at the proposed commercial site, Tokushima, with batch size of the proposed commercial Batch size-2.

<b>Tablet Strength</b>	<b>Lot No.</b>		
0.25-mg	11G74A0025	11G75A0025	11G76A0025
0.5-mg	10J91A0050A	10J91A0050B	10J91A0050C
1-mg	10J96A001A	10J96A001B	10J96A001C
2-mg	10K70A002A	10K70A002B	10K70A002C
3-mg	10K74A003A	10K74A003B	10K74A003C
4-mg	11G77A004	11G80A004	11G81A004

Below are the impurity profile, content uniformity and dissolution results of these batches.

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**EVALUATION:** Adequate. Results of all batches were within specifications. The impurity level was below the quantitation limit of (b) (4). The content uniformity of the tablets are acceptable and the lowest strength, 0.25 mg, tablets is equally good as the highest strength, 4 mg, tablets.

#### P.5.5 Characterization of Impurities

The degradation products detected in tablets are (b) (4).

**P.5.6 Justification of Specification(s)**

Appearance – The acceptance is based on the description of each strength of the (b) (4) tablets.

Identification – A HPLC method (b) (4) is used for the identification of the product. The UV spectrum of the sample must match that of brexpiprazole reference standard

Impurities/degradation products – The acceptance limits for (b) (4) (b) (4) and other individual impurities comply with ICH Q3B guidance.

Content uniformity – This is the current USP <905> requirement.

NDA #-###

Drug Product Name

Assay – The acceptance limit of (b) (4) of the % label claim is established based on the batch analysis data, accuracy and precision of the analytical method and the stability of the drug products.

Dissolution – The specification is  $Q = (b) (4)$  in 30 minutes.

Microbial limit – The acceptance criteria for the aerobic microbial count, total combined yeasts/moulds count and the absence of *Escherichia coli* are in compliance with those specified in the USP general chapter <111>.



**Evaluation:** Adequate. It is adequate with all justifications provided except the ID test (the applicant agreed to add a second ID test method to the specification (see section P.5.1 – Specification for the evaluation and comments on the acceptance of the product specifications). The rationales provided (b) (4) from drug product specification is acceptable.

#### P.6 Reference Standards or Materials

The applicant referred this section to Section 3.2.S.5. Only brexpiprazole reference standard is used and the current lot number is S12G74. There are no mention of the reference standards for the impurities (b) (4).

**Evaluation:** Adequate. (b) (4)

#### P.7 Container Closure System

Brexpiprazole tablets are packaged in (b) (4) high density polyethylene (HDPE) bottles (b) (4).

##### HDPE Bottles

NDA #-###

Drug Product Name

Brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets are packaged into <sup>(b) (4)</sup> high density polyethylene (HDPE) bottles, <sup>(b) (4)</sup>. Each bottle contains 30 tablets.

<sup>(b) (4)</sup>

All components <sup>(b) (4)</sup> are regulated by the Food and Drug Administration as indirect food additives under appropriate paragraphs of the Code of Federal Regulations, Title 21.

The applicant provided purchase specification and test methods for the HDPE bottle and closure components. Test items included appearance, identification and dimension with acceptance criteria.

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**Final Evaluation:** Adequate. The responses are acceptable.

## **P.8 Stability**

### **P.8.1 Stability Summary and Conclusion**

Stability studies were conducted on production-scale brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets packaged in the proposed commercial packages, high density polyethylene (HDPE) bottle (b) (4) as described in the below table.

Overview of stability program for brexpiprazole 0.1-, 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets (number of batches)



Registration batch numbers

Tablet Strength	Lot No.	API Lot No.	Mnfg Scale
0.25-mg	11G74A0025	C10H86 (3/3) M	(b) (4)
	11G75A0025	C10K71M	
	11G76A0025	C10K81M	
0.5-mg	10J91A0050A	C10H92M	
	10J91A0050B	C10H95M	
	10J91A0050C	C10H00M	
1-mg	10J96A001A	C10H92M	
	10J96A001B	C10H95M	
	10J96A001C	C10H00M	
2-mg	10K70A002A	C10H92M	
	10K70A002B	C10H95M	
	10K70A002C	C10H00M	
3-mg	10K74A003A	C10H92M	
	10K74A003B	C10H95M	
	10K74A003C	C10H00M	
4-mg	11G77A004	C10H86 (3/3) M	
	11G80A004	C10K71M	
	11G81A004	C10K81M	

Stability summary and conclusion:

- The applicant mentioned that brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets are stable products when packaged in the proposed commercial packages and stored at 25°C/60% RH for 24 months, (b) (4)  
 Also, accelerated stability studies at 40°C/75% RH have completed, and no significant changes were observed.

NDA #-###

Drug Product Name

- The results of the photostability studies indicate that neither the exposed product nor the product packaged in the proposed commercial packages is sensitive to high-intensity fluorescent light or UVA irradiation.
- The data (b) (4) demonstrate the stability of brexpiprazole tablets to humidity.
- The data (b) (4) indicate that the product is not affected by temperature excursions.
- The data (b) (4) demonstrate the stability of the brexpiprazole to heat.
- All test results met the stability specifications except for impurities/degradation products. After 3 months, the amount of an impurity (b) (4) slightly exceeded the limit for 0.25- and 0.5-mg tablets, however, below the ICH qualification threshold. All strengths are stable for 3 months stored at 50°C.
- The applicant mentioned that an unknown substance (b) (4) was reported in the stability report which was identified as (b) (4) after the completion of the stability study.

Labeled storage condition and shelf-life:

The applicant proposed an expiry date of 36-month for 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets when packaged in the proposed commercial packages of HDPE bottles (b) (4) with the following label statement:

“Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F)”

**Evaluation:** Adequate. The available 24 months stability data supports the proposed 36 month expiry dating. Below are the evaluation of the stability results.



## **II. Results on registration batches in HDPE bottles:**

The followings are the summary of the results of the registration batches packaged in HDPE bottles:

The strengths of the tablets placed on stability are 0.25 mg and 4 mg.

NDA #-###

Drug Product Name

Appearance – All drug product stability samples of both strengths at all storage conditions and test time points met specification.

Assay - All drug product stability samples of both strengths at all storage conditions and test time points met specification. There is no trend observed in the assay results.

Impurities –



(b) (4)

Dissolution – The dissolution profiles of the tablets in the HDPE bottles are very similar to the profile of the tablets (b) (4).

Microbial limit test - Results of all stability samples at (b) (4) storage conditions for all batches of both strength tested at 12 and 24 months met specification.



(b) (4)

### III. Results on bulk tablets stability study:



(b) (4)

All test results were within specifications.

(b) (4)



(b) (4)

### IV. Results on stressed storage conditions study:

The strengths of the tablets placed on stressed conditions stability are:

NDA #-###

Drug Product Name

(b) (4)

**V. Results on photostability study:**

All (b) (4) 0.25- and 4-mg tablets packaged in HDPE bottles were used for the photostability study. All test results were within specifications. No impurity was observed in the photostability study.

**VI. Results on freeze-thaw stability study**

All (b) (4) 0.25- and 4-mg tablets packaged in HDPE bottles were used for the freeze-thaw stability study. All test results were within specifications. No impurity was observed in the samples in the freeze-thaw cycling studies. (b) (4)

**VII. Other comments:**

The internal acceptance criteria in the stability program for individual impurity and dissolution are tighter than those in the release testing. The tighter internal acceptance need not be incorporated in the drug product specification.

Although the method numbers for the assay, impurities and dissolution HPLC method are different from those stated in the drug product specification, all the HPLC conditions are identical.

**P.8.2 Postapproval Stability Protocol and Stability Commitment**

The applicant commits that:

- Formal stability studies on 0.25-, 0.5-, 1-, 2-, 3- and 4-mg tablets manufactured at production scale, will be completed according to ICH Q1A (R2).
- Otsuka Pharmaceutical Co., Ltd. commits that at least one lot each year of each strength of the product in each container/closure system manufactured at the proposed commercial manufacturing site will be placed in the Marketed Product Stability Testing Program according to the protocol described below. Results of the stability studies will be submitted in the annual report.

**Evaluation:** Adequate. The marketed product stability testing protocol is acceptable since the registration batches were manufactured at the proposed commercial manufacturing site and in the proposed larger batch size, Batch size-2.

### P.8.3 Stability Data

The sponsor provided the stability data in table format. See discussion on the stability results in Section P.8.1 - Stability Summary and Conclusion.

(b) (4)

**Evaluation:** Adequate

## A APPENDICES

### A.1 Adventitious Agents Safety Evaluation

Magnesium stearate (b) (4). Lactose monohydrate (b) (4) and the applicant provided a copy of the declaration/certificate of suitability obtained from the supplier of the lactose monohydrate.

NDA #-###

Drug Product Name

**Evaluation:** Adequate.**A.2 Novel Excipients**

No novel excipient is used in the formulation of brexpiprazole tablets.

**Evaluation:** Adequate.**R REGIONAL INFORMATION****R1 Executed Batch Records**

The applicant provided master manufacturing batch records for the following batches:

- Clinical trial batch for BE study, 1mg tablets, batch size (b) (4)
- LTSS batch, 0.25 mg tablets, (b) (4)
- LTSS batch, 0.5-, 1-, 2-, 3- and 4-mg tablets, (b) (4)

**Evaluation:** Adequate. The process parameter (b) (4) for the LTSS batches written in the master batch records are the same as those stated in the manufacturing process flowchart.

**R2 Comparability Protocols**

(b) (4)



**Evaluation – Adequate.**

**R3      Methods Validation Package**

The applicant included the method validation package in the submission. A consult for methods validation on HPLC assay and impurities testing for drug substance and drug product has been sent to the Division of Pharmaceutical Analysis.

**II.      Review Of Common Technical Document-Quality (Ctd-Q) Module 1**

NDA #-###

Drug Product Name

**A. Labeling & Package Insert****Highlights of Prescribing Information**

Trade Name:

Established Name: Brexpiprazole

Indication: Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and treatment of schizophrenia.

Dosage and Administration:

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD (2.1)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia (2.2)	1 mg/day	2 to 4 mg/day	4 mg/day

Dosage Form and Strengths: Tablets, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

**Evaluation:** Adequate. The CMC related information provided is sufficient and accurate.**Full Prescribing Information**1. Indication:

PRODUCT is indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and for the treatment of schizophrenia.

3. Dosage Forms and Strength:

The PRODUCT tablets are available in the following strengths:

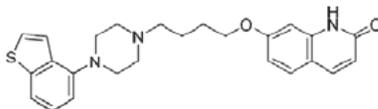
Tablet Strength	Tablet Color/Shape	Tablet Markings
0.25 mg	Light brown Round; shallow convex; bevel-edged	"BRX" and "0.25"
0.5 mg	Light orange Round; shallow convex; bevel-edged	"BRX" and "0.5"
1 mg	Light yellow Round; shallow convex; bevel-edged	"BRX" and "1"
2 mg	Light green Round; shallow convex; bevel-edged	"BRX" and "2"
3 mg	Light purple Round; shallow convex; bevel-edged	"BRX" and "3"
4 mg	White Round; shallow convex; bevel-edged	"BRX" and "4"

11. Description:

Brexpiprazole is a serotonergic-noradrenergic-dopaminergic acting compound that is available as TRADEMARK (brexpiprazole) Tablets. Brexpiprazole is 7-{4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one. The empirical formula is C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S and its molecular weight is 433.57. The chemical structure is:

NDA #-###

Drug Product Name



TRADEMARK Tablets are available in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg strengths. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc. Colorants include titanium dioxide, iron oxide and ferrous ferric oxide.

16. How Supplied/Storage and Handling:

PRODUCT (brexpiprazole) tablets are non-scored have markings on one side and are available in the following strengths and package configurations:

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
0.25 mg	light brown round, shallow convex; bevel-edged	“BRX” and “0.25”	Bottle of 30 HUD of 50	59148-035-13 59148-035-65
0.5 mg	light orange round, shallow convex; bevel-edged	“BRX” and “0.5”	Bottle of 30 HUD of 100	59148-036-13 59148-036-35
1 mg	light yellow round, shallow convex; bevel-edged	“BRX” and “1”	Bottle of 30 HUD of 100	59148-037-13 59148-037-35
2 mg	light green round, shallow convex; bevel-edged	“BRX” and “2”	Bottle of 30 HUD of 100	59148-038-13 59148-038-35
3 mg	light purple round, shallow convex; bevel-edged	“BRX” and “3”	Bottle of 30 HUD of 100	59148-039-13 59148-039-35
4 mg	white round, shallow convex; bevel-edged	“BRX” and “4”	Bottle of 30 HUD of 100	59148-040-13 59148-040-35

(b) (4)

NDA #-###

(b) (4)

**Storage:**

Store PRODUCT tablets at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F).  
Keep out of reach of children.

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

**Evaluation:** Adequate. The CMC related information provided is sufficient and accurate.  
Details will be discussed during labeling review meetings. The PRODUCT (trade name) will be replaced by the DMEPA approved trade name.

**Container labels:**

Below are the container labels for the 0.25 mg tablets provided in Amendment #0009 dated 10/14/14). The container labels for the 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg are the same as those of 0.25 mg except the tablet strength is different.

**Immediate container label for 0.25 mg tablets (Amendment #0009):**

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**Evaluation:** Adequate. The bottle (b) (4) label sample contains the following required information: Rx only; NDC number (XXXXXX-XXX-XX); number of tablets, the trade name and established name; the potency; the company name, Otsuka Pharmaceutical Co., and address; lot number and expiration date; storage condition. The warning statement, Keep out of reach of children and barcode are also included in the label. Details of the container labels (b) (4) will be discussed with DMEPA in labeling meetings.

#### **B. Environmental Assessment Or Claim Of Categorical Exclusion**

The applicant mentioned that brexpiprazole, a new active substance, in this NDA meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31(b). To the best knowledge of Otsuka Pharmaceutical Co., Ltd., no extraordinary circumstances exist [21 CFR 25.15 (d)]. This drug is manufactured using a synthetic process and is not known to be derived from any wild-sourced plant and/or animal material. The applicant also provided the following estimated Environmental Introduction Concentration based on the US market estimated total production volume of brexpiprazole (b) (4).

NDA #-###

Drug Product Name

Environmental Introduction Concentration - Based on the volume (b) (4) for brexpiprazole, the maximal Expected Introduction Concentration (EIC) is 0.224 ppb, as calculated according to the FDA's guidance.

$$\text{EIC-Aquatic (ppb)} = A \times B \times C \times D$$



**Evaluation:** Adequate.

### III. List Of Deficiencies To Be Communicated

None. All deficiencies have been satisfactorily resolved.

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# INSPECTIONAL ASSIGNMENT

(EMAIL TRANSMITTAL)

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**Date:** November 30, 2014

**To:** Division of Medical Products and Tobacco Inspections  
Office of Regulatory Affairs

**Facility:** Otsuka Pharmaceutical Co Ltd,  
5006-5, Aza Higashiyama, Omagari,  
Yoshinogari-cho, Kansaki-gun, Saga 842-0197, Japan  
FEI 3003808559

**Drug Name  
(dosage form,  
strength/concentration):** (b) (4) (brexpiprazole) Tablets; 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3  
mg, and 4 mg

**Profile Class:** CSN

**A/NDA No.:** NDA 205-422

**CMC Reviewer** Wendy I. Wilson-Lee, Ph.D.  
CDER/OPS/ONDQA  
[wendy.wilson@fda.hhs.gov](mailto:wendy.wilson@fda.hhs.gov) Tel: 301-796-1651

**Microbiology Reviewer (if  
applicable)** N/A

**OC Compliance Officer** Linda Ng, Ph.D.  
CDER/OC/OMPQ, HFD-320  
[linda.ng@fda.hhs.gov](mailto:linda.ng@fda.hhs.gov) Tel: 301-796-1426

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CDER has identified specific area(s) for inspectional focus for drug substance manufacturing in connection with the NDA 205-422. In accordance with the Pre-Approval Inspection Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug substance by focusing on areas in which data is questionable; drug characteristics or sensitivities<sup>1</sup> indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

### Summary of Product and Manufacturing Process:

The administrative office for Otsuka Pharmaceutical Co, Ltd is located at 463-10 Kagasuno,

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<sup>1</sup> Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

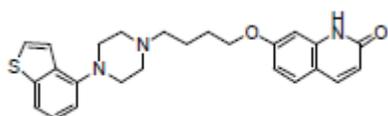
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(b) (4) (brexpiprazole) Tablets; 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

Kawauchi-cho, Tokushima-shi, Tokushima, Japan. The manufacturing facility, FEI 3003808559, termed Saga Factory is located at 5006-5, Aza Higashiyama, Omagari, Yoshinogari-cho Kansaki-gun, Saga 842-0197. Mr. Tomonori Nakagawa of the Quality Control Department is the facility's contact person. Otsuka Pharmaceutical Co, Ltd is also the sponsor of the NDA.

The drug substance Brexpiprazole is a new molecular entity (b) (4). The drug substance manufacturing process and testing are performed at two facilities in Japan. The other facility, Second Tokushima Factory, owned by Otsuka, FEI 3004007378, is located at 224-18, Hirashi Ebisuno, Kawauchi-cho, Tokushima-shi, Tokushima 771-0182, Japan.

Brexpiprazole is stable under stressed conditions and storage conditions of (b) (4). It has been assigned a re-test period of (b) (4) years when stored below 30°C.



Brexpiprazole

Molecular Weight = 433.57

Molecular Formula = C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S

The drug product is a (b) (4) immediate release oral tablet formulations of 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg strength. The indication is for the treatment of major depression disorder. All strengths of proposed commercial tablets are of the same shape (round), and same (b) (4) total weight of 93 mg. The product will be supplied in 30-count high density polyethylene (HDPE) bottles (b) (4).

### Manufacturing Process:

(b) (4) Details are provided in Appendix I for the flow chart of the chemical synthesis, and in Appendix II for the scale differences between the two API facilities and ranges of the manufacturing steps. Appendix III provides the critical process parameters (CPP) for each of the synthetic steps. A discussion of the potential critical quality attributes (CQA) of brexpiprazole is summarized in Appendix IV with impact in Appendix V. Appendix VI contains the specification of the API and Appendix VII illustrates a representative chromatogram of brexpiprazole and its impurities with structures. Appendix VIII describes the site specific considerations of the two Japanese API facilities, Saga and Second Tokushima.

Appendices IV to VI and Appendix VIII were abstracted from the Product Quality Memo (PQM) provided by Dr. Wendy Wilson.

(b) (4)

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**The following is a brief explanation of product or process specific issues that should receive follow-up during the inspection.**

### **I. Chemistry Review**

CMC chemist, Wendy Wilson, Ph.D., has been assigned to review the drug substance section of this application. She has provided a PQM dated November 14, 2014, and additional comments via email dated November 19, 2014. All comments are included below.

Her comments for the drug substance from her PQM and email are reproduced below:

- Brexpiprazole ( $C_{25}H_{27}N_3O_2S$ ) has a molecular weight of 433.57. (b) (4)  
(b) (4)
- Risk assessment of process parameters in each manufacturing step was conducted. The initial assessment included identifying the potential critical quality attributes, assessment of the impact of the manufacturing process on the potential CQAs, identifying the risk factors, and identifying potential critical process parameters that impact the risk factors. A risk level was defined for each drug substance manufacturing step. Based on the initial assessment, drug substance manufacturing Steps 1 – 4 were identified as critical process steps and critical process parameters were defined for each step. Design spaces for some critical process parameters were established for Steps 1, 2, and 3. Both manufacturing sites will manufacture using the design spaces for control of the designated critical process parameters.  
[OC: See comments below for CQAs, CPPs and design spaces]\
- The Second Tokushima Site was used to manufacture the registration drug substance

batches. Otsuka is proposing an additional commercial site for drug substance manufacturing, the Saga site. The sponsor provided comparability data to support this site as a commercial site. The investigator might want to confirm that the process and associated knowledge was transferred successfully from the Second Tokushima site to the Saga site.

- There is a manufacturing scale difference between the two drug substance sites with the Saga site having a larger manufacturing capacity. The scale-up at the Saga site might be of interest during the inspection.

[OC: Also see III.a.iii and Appendix II]

- Otsuka is proposing design spaces for several of the process parameters associated with the drug substance manufacturing. Appendix II highlights which parameters will be controlled by design spaces. The investigator might want to confirm that the Saga site is ready to manufacture based on these design spaces. An evaluation of the quality systems at both sites might also be useful to determine if it can handle flexible manufacturing conditions.

[OC: Not all the details are clear. Design spaces are included (b) (4)

(b) (4) Discussion is provided in Section 3.2.S.2.6. The firm will be asked to clarify and expand on details during inspection. Also see III.a.ii]

- The applicant proposes (b) (4) No other info is included in the submission to support this proposal. Evaluation of criteria used to determine which method should be used might be an inspectional consideration
- The applicant's proposal for annual drug substance stability batches calls for testing on an annual basis only instead of the traditional 3, 6, 9, 12, 18, 24, etc. protocols. Evaluation of how product quality will be assured post-release, at least early on, might be an inspectional consideration given the limited commercial production experience  
[OC: The stability data should be evaluated for equivalency to data from Second Tokushima site since some comparability data from the Saga Site was submitted to the application. See also IV.d.i]

## II. Microbiology Review

This section is not applicable since this is not a sterile product.

## III. Manufacturing

The comments above from the CMC reviewer should be evaluated during inspection.

**a. Processing Conditions**

- i. The analytical procedures for the in-process testing of the intermediates/drug substance require use of light resistant containers (b) (4). Evaluate if vessels and transfers are controlled and protected from light.
- ii. Design spaces for control of reaction temperatures are proposed for Steps 2 and 3. Evaluate what the design spaces are, how these are controlled, at what target process parameter settings and if they are within the design spaces. Determine how the facility controls process parameter changes within and outside of the design space.
- iii. Appendix II provides the size differences between the Saga facility and the Second Tokushima facility for the various steps. It gives a range with the median at (b) (4) commercial size. Evaluate what the actual plans or intended target for batch size. (b) (4)

**b. Hold Times during Processing**

- i. It is not clear if the manufacturing process has any hold time during processing. Evaluate if validation is performed for hold as appropriate.

**c. Preparation of Final API**

- (b) (4)
- ii. Examine the temperature conditions and reaction rate time of the manufacturing process described in the flow chart of Appendix I and the executed batch record, if these are consistent in their manufacturing process in the master batch record.
  - iii. The particle size of API plays a role in the dissolution of the final drug product. Evaluate how the particle size is controlled for release and stability.

**IV. Quality Control / Quality Assurance**

**a. Quality System**

- i. Determine if any OOS results or deviations or rejections have occurred during development or production of submission batches, and report on adequacy of

investigations and corrective actions.

ii. Evaluate how the firm tracks and trends process data. Take an existing process and evaluate if the process and product are periodically evaluated to determine if it is in a state of control or if there is a need to change drug product specifications or manufacturing or control procedures (such as changes in equipment process control or operating ranges)? How is the control strategy updated throughout the lifecycle of the process?

iii. The API batch analysis data submitted in the application are for lot #100823, 100826 and 100831, and are not sequential. Examine how the batches are numbered and evaluate handling of failures or discards of batches.

**b. Qualification/Validation**

i. Determine if cleaning records are available to verify the proper cleaning of the equipment before the use. Although cleaning validation studies are not required prior to approval of the application, please review and determine the adequacy of any cleaning validation data that may be available for the receiving vessel. Also, SOPs, particularly with regard to time limitations between batches and for cleaning have been found deficient at many manufacturers. Review the cleaning SOPs, including drawings and validation data with regard to cleaning and sanitization.

ii. Review the process validation protocol (i.e., process performance qualification) which specifies the procedures (and tests) to be conducted and the data to be collected. Determine if the plan includes an evaluation of the suitability of materials and an evaluation of consistent adherence to pre-established process parameters and quality attributes. Review any available data to determine if acceptance criteria in the PPQ protocol are being met. Determine if these studies were conducted at commercial scale, using the proposed commercial equipment, and conforming to the proposed commercial process.

**c. Raw Materials**

i. A number of raw materials and residuals are controlled by design spaces. Confirm that the target within the design spaces is met.

ii. Audit the raw material documents and determine if the firm has qualified all suppliers for incoming raw material. Also, evaluate if incoming raw material quality control testing is sufficient for the raw material(s) selected for audit.

**d. Stability**

i. Brexpiprazole is a new molecular entity. The Saga site is an alternate site. Evaluate if any batches manufactured at this site have been placed on stability. Stability data submitted to the application came from the Second Tokushima facility.

**e. Distribution Supply Chain**

- i. Determine if the firm's quality system ensures that its Quality Control Unit (QCU) approves all suppliers and knows the identity of the manufacturer (not only the distributor) of all of its ingredients. All ingredients need to be received from manufacturing sources that are approved and qualified by QCU, and from a reliable supply chain.
- ii. Otsuka is an international firm with multiple international sites. Evaluate if shipping qualification data are available at this site to support such activities. It is not clear which facility will hold such data.

A pre-inspection briefing will be scheduled prior to the inspection. Should you have questions prior to, during or post inspection, please contact the CDER official identified above.

Please report your findings regarding these issues in the Establishment Inspection Report (EIR) under the heading, "ADDITIONAL INFORMATION" with the subheading, "Follow-up to CDER PAI Questions."

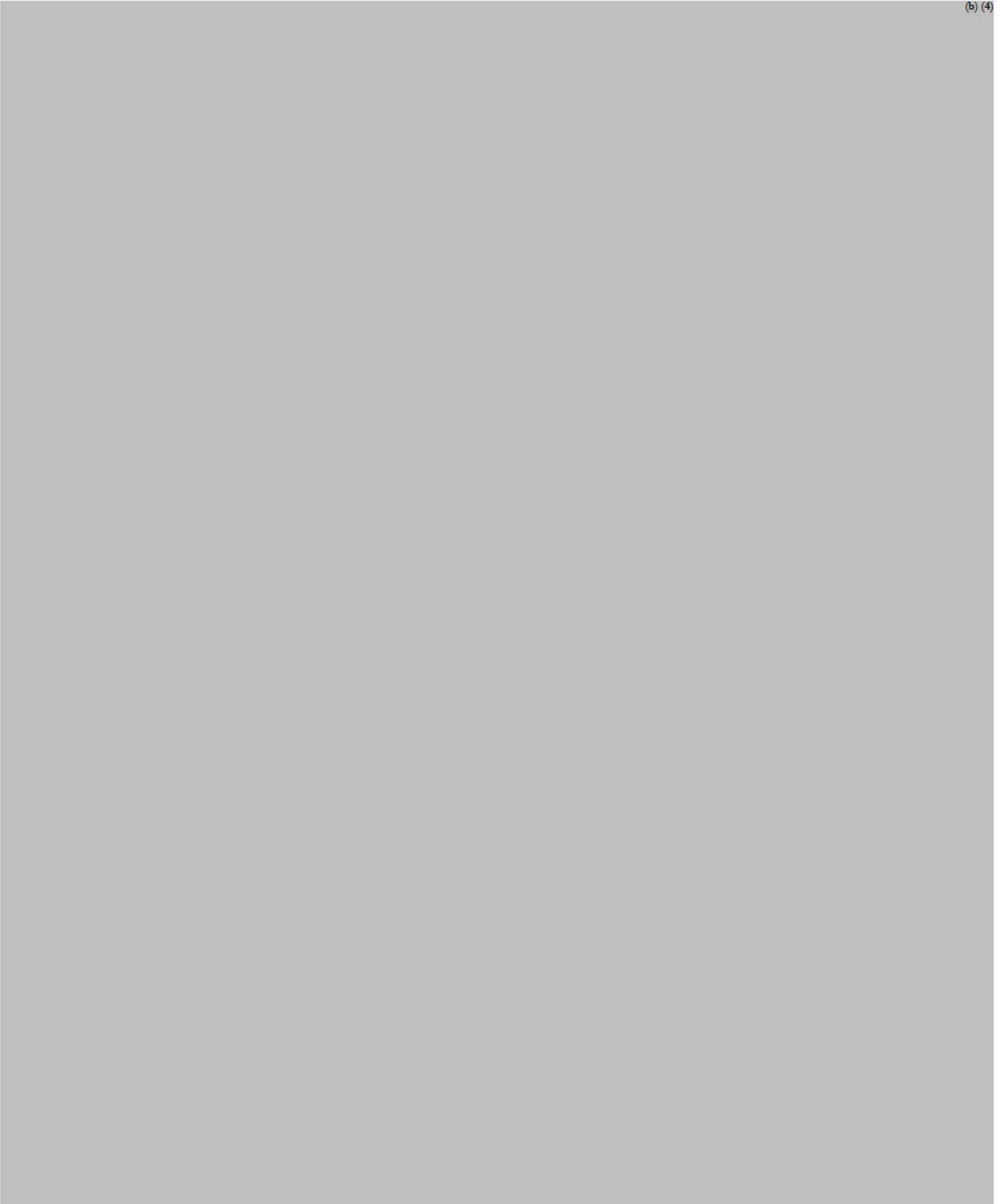
**THIS ASSIGNMENT IS CONFIDENTIAL FDA CORRESPONDENCE**

cc:  
HFD-323 (New Drug Manufacturing Assessment Branch)  
Wendy Wilson, Ph.D., ONDQA  
Thomas Wong, Ph.D., ONDQA  
Mahesh Ramanadham, Pharm D., OMPQ

(b) (4) (brexpiprazole) Tablets; 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

Juandria Williams, Ph.D., OMPQ  
Uduak Inokon, (b) (4) HFR-PA160  
OC Doc. No.: KTM-2014-023

**APPENDIX I. Chemical Synthesis Flowchart for brexpiprazole**



**APPENDIX IV. Potential CQAs of Brexpiprazole**

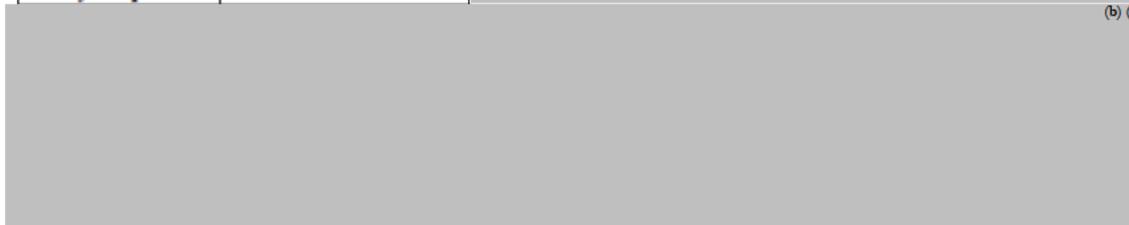
<b>Table 3.2.S.2.6.2.1-1 Potential Critical Quality Attributes of Brexpiprazole Drug Substance</b>			
<b>Attribute</b>	<b>Test Item</b>	<b>Critical or not Critical</b>	<b>Rationale</b>
Description	Description	Not critical	ICHQ6A <sup>a</sup> test item that needs to be included in the specification
Identification	UV, IR, HPLC	Not critical	ICHQ6A test item that needs to be included in the specification
Assay	Assay tests	Not critical	ICHQ6A test item that needs to be included in the specification
Purity	Heavy metals	Critical	(b) (4)
	(b) (4)	Critical	
	Drug-related impurities	Critical	ICHQ6A Flow Chart #1 test item that needs to be included in the specification
	Residual solvents	Critical	Organic solvents are used in the manufacturing process.
	Genotoxic impurities	Critical	Genotoxic impurities are identified
	Residue on ignition	Critical	(b) (4)
Physicochemical property	Melting point	Not critical	(b) (4)
Particle size	Particle size	Critical	ICHQ6A Flow Chart #3 Particle size has an impact on the dissolution profiles of the drug product.
Polymorphism	---	Critical	ICHQ6A Flow Chart #4 (b) (4)
Optical activity	---	Not critical	ICHQ6A Flow Chart #5 Brexpiprazole drug substance is not chiral. (b) (4)
(b) (4)			
Microbial limit	---	Not critical	ICHQ6A Flow Chart #6 No microbial growth was observed during the developmental stage.

<sup>a</sup>Test Procedures and Acceptance Criteria for New Drug Substance and New Drug Product: Chemical Substances

**APPENDIX V. Impact of Each Manufacturing Step & Physical Properties on CQAs**

<b>Table 3.2.S.2.6.2.2-1 Impact of Each Manufacturing Step on CQAs of Brexpiprazole Drug Substance</b>						
<b>Critical Quality Attribute</b>	<b>Test Item</b>	<b>Step 1</b>	<b>Step 2</b>	<b>Step 3</b>	<b>Step 4</b>	<b>Step 5</b>
Purity	Heavy metals	(b) (4)				
	(b) (4)					
	Drug-related impurities					
	Residual solvents					
	Genotoxic impurities					
Residue on ignition						
Particle size	----					
Polymorphism	----					

<b>Table 3.2.S.2.6.2.3-1 Physical Properties Related to Critical Quality Attributes of Drug Substance</b>						
<b>Critical Quality Attribute</b>	<b>Test Item</b>	<b>Step 1</b>	<b>Step 2</b>	<b>Step 3</b>	<b>Step 4</b>	<b>Step 5</b>
Purity	Heavy metals	(b) (4)				
	(b) (4)					
	Drug-related impurities					
	Residual solvents					
	Genotoxic impurities					
Residue on ignition						
Particle size	----					
Polymorphism	----					



### APPENDIX VI. Brexpiprazole Specification

Test Item	Acceptance Criteria	Test Method
Description	(b) (4)	Visual
Identification by UV	The UV spectrum of the sample is comparable to that of the reference standard	UV
by IR	The IR spectrum of the sample is comparable to that of the reference standard	IR
Melting point	(b) (4)	JP
Heavy metals	(b) (4)	USP
(b) (4)	(b) (4)	AAS <sup>a</sup>
Drug-related impurities by HPLC	(b) (4)	HPLC
(b) (4)	(b) (4)	HPLC <sup>a</sup>
(b) (4)	(b) (4)	GC <sup>a</sup>
Residual solvents by GC	(b) (4)	GC
(b) (4)	(b) (4)	(b) (4)
Residue on ignition	(b) (4)	JP <sup>b</sup>
Assay by HPLC	(b) (4)	HPLC
Particle size distribution	Mean particle size: (b) (4) (b) (4) of the particles: (b) (4)	JP <sup>b</sup>

JP = Japanese Pharmacopoeia; USP = US Pharmacopoeia; AAS = atomic absorption spectrophotometry  
(b) (4)

<sup>b</sup> harmonized USP/PhEur/JP

**APPENDIX VII. HPL Chromatogram of Brexpiprazole and Impurities**

(b) (4)



**APPENDIX VIII. Site Specific Information for the Two API Facilities**

**Second Tokushima Factory**

<b>Site Specific High Risk Elements of the Manufacturing Process and Control Strategy</b>	<b>Site Specific Considerations for Inspection</b>
Design spaces proposed for control of (b) (4) (b) (4) Step 1 (refer to Section 3.2.S.2.6.2); No BPR for drug substance manufacturing was provided in the submission	Implementation of the control strategy utilizing design spaces at the manufacturing site is critical , - Please confirm if target values established for critical process parameters are within the proposed design spaces

	- Assessment of adequacy of documentation within the Quality System to manage movements of the target process parameter settings within the proposed design space
Design spaces proposed for control of (b) (4) Step 2; (b) (4) (refer to Section 3.2.S.2.6.2); No BPR for drug substance manufacturing was provided in the submission,	-same as above
Design spaces proposed for control of (b) (4) Step 3 (refer to Section 3.2.S.2.6.2); No BPR for drug substance manufacturing was provided in the submission	--same as above
(b) (4) starting material synthesized from different processes by different suppliers with different impurity profiles; proposed (b) (4) specification and analytical procedures considered able to detect all impurities regardless of supplier or synthetic route	Adequacy of in-house procedures to assure consistent quality (b) (4)
(b) (4) testing proposed (b) (4) in the final (b) (4) drug substance; (b) (4)	-Availability of any on-site data and associated procedures to support (b) (4) testing (b) (4)

**Saga Factory**

<b>Site Specific High Risk Elements of the Manufacturing Process and Control Strategy</b>	<b>Site Specific Considerations for Inspection</b>
Same as Second Tokushima Factory	The Saga site is a new site proposed for commercial manufacturing; Registration stability batches were manufactured at the Second

	<p>Tokushima site; Saga site differs in equipment type and scale (b) (4) increase in manufacturing capacity) compared to the Second Tokushima site; The (b) (4) control strategy, including design spaces, should be the same for both sites; evaluate if the difference in manufacturing scale were incorporated into the risk assessment</p>
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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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LINDA L NG  
12/01/2014

MAHESH R RAMANADHAM  
12/01/2014

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

## IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205422**

### DATES AND GOALS:

Receipt Date: 07/11/14

Mid-Cycle: 12/11/14 (hold mid-cycle meeting by)

Post-Mid-Cycle Meeting/Communication with Sponsor (by 12/25/14)

Late-Cycle Meeting 03/30/15 (send Briefing Pkg ~ 20 days ahead if AC; 2 days if no AC)

[Review Due Dates: to TLs (3/11/15); CDTL (3/19/15); DD (5/30/15); OD (6/20/15)]

Action Date: 07/10/15

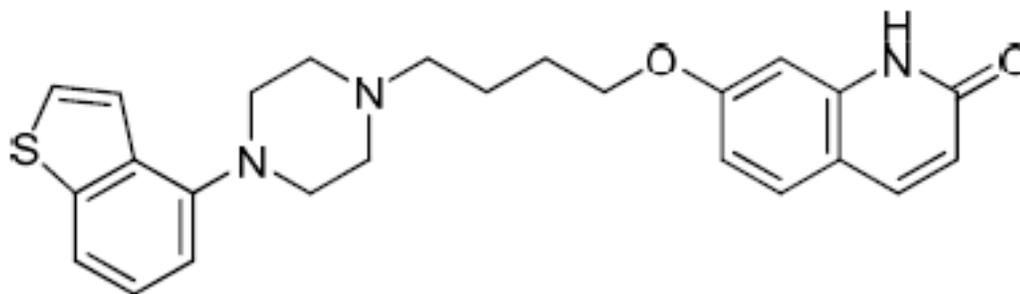
PDUFA Date: 07/11/15 (Saturday)

### 2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN):	Brexpiprazole
Dosage Form:	Tablets
Route of Administration	Oral
Strength/Potency	0.25, 0.5, 1, 2, 3 and 4 mg
Rx/OTC Dispensed:	Rx

3. INDICATION: MDD and schizophrenia

### 4. DRUG SUBSTANCE STRUCTURAL FORMULA:



5. NAME OF APPLICANT (as indicated on Form 356h): Otsuka.

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

**6. SUBMISSION PROPERTIES:**

Review Priority:	Standard Review	Priority Review	Expedited Review Requested	Expedited Review
Submission Classification (Chemical Classification Code):	1			
Application Type:	505(b)(1)			
Breakthrough Therapy	N			
Responsible Organization (Clinical Division):	DPP			

**7. CONSULTS:**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		
Pharmacology/Toxicology	x		Impurity limits
Methods Validation	x		
Environmental Assessment		x	EA exclusion claimed
CDRH		x	
Other			

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

## Overall Filing Conclusions and Recommendations

### CMC:

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b> Yes
CMC Filing Issues: None
1.

<b>Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?</b> No
CMC Comments for 74-Day Letter: None
1. No

### Biopharmaceutics:

<b>Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?</b> Yes                      No
Biopharmaceutics Filing Issues:
1. None

<b>Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?</b> Yes                      No
Biopharmaceutics Comments for 74-Day Letter:
Yes: Provide the PK parameter analysis datasets as SAS transport files for bioequivalence studies 209 and 243, preferably in stacked column format.

### Microbiology:

<b>Is the Product Quality Section of the application fileable from a Microbiology perspective?</b> Yes                      No
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

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

**Summary of Initial Quality Assessment**

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
n	y	n	

Is a team review recommended?	Yes	No
Suggested expertise for team:		

**Summary of Critical Issues and Complexities**

**Risk Assessment:**

Product Property/Impact of change/CQAs	Factors affecting CQA	O	S	D	FMECA RPN	Comment
Assay/stability		1	2	3	6	Very stable product
Solid state	(b) (4)	3	3	4	36	(b) (4)
Content Uniformity		3	4	4	48	
Microbial		1	2	3	6	
Dissolution		4	2	4	32	

RPN < 25 is considered **low**  
RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.

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

**Initial Quality Assessment**

Otsuka is seeking approval to market 0.25, 0.5, 1, 2, 3, and 4 mg (b) (4) immediate release oral tablet formulations of Brexpiprazole, an NME, for the treatment of major depression disorder and schizophrenia. The product will be supplied in 30-count HDPE bottles (b) (4)

**DRUG SUBSTANCE**

Brexpiprazole is an

BSC Class 2.

(b) (4) Its structure is related to that of the widely-marketed aripiprazole.

Two drug substance manufacturing sites are proposed – Second Tokushima and Saga sites – both in Japan.

Batch analysis data indicate significantly lower impurity levels in more recent batches than those manufactured earlier in development.

CPPs and the results of a risk assessment were listed for each process step.

Typical chemical and solid state characterization data were provided. The impurity profile of material from both sites was stated to be similar – this will require evaluation. The drug substance specification is reproduced below. The drug substance reviewer should consult with the drug product reviewer over the appropriateness of the particle size distribution

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

acceptance criteria. Data appear to indicate a significant slowing of in vitro dissolution profile as the mean particle size approaches (b) (4) um (Figure 3.2.P.2.2.1.-2). (b) (4)

Test Item	Acceptance Criteria	Test Method
Description	(b) (4)	Visual
Identification by UV	The UV spectrum of the sample is comparable to that of the reference standard	UV
Identification by IR	The IR spectrum of the sample is comparable to that of the reference standard	IR
Melting point	(b) (4)	JP
Heavy metals	(b) (4)	USP
(b) (4)		AAS <sup>a</sup>
Drug-related impurities by HPLC		HPLC
(b) (4)		HPLC <sup>a</sup>
(b) (4)		GC <sup>a</sup>
(b) (4)		GC
(b) (4)		(b) (4)
Residue on ignition		JP <sup>b</sup>
Assay by HPLC		HPLC
Particle size distribution		JP <sup>b</sup>

A (b) (4) year retest period is proposed based on 24 months data from drug substance produced at the Second Tokushima site. Comparability data were provided to support the same retest period for material from the Saga site where data up to nine months were provided. .

**DRUG PRODUCT**

Each strength of proposed commercial tablets has the same shape (round), and same (b) (4) total weight of 93 mg. Lactose monohydrate (b) (4)

The excipients are typical of an IR (b) (4) tablet – all are USP/NF grade (except for colorants). The strengths are differentiated by the (b) (4) color and debossing. (b) (4) The applicant states that a similar process has been in place throughout development. (b) (4)

(b) (4) future risk to drug product quality of this more critical quality attribute. (b) (4)

. The DoE and the resulting proposed process ranges will require evaluation. (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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“To provide a flexible manufacturing to address market demands” two batch sizes are proposed. (b) (4). Data supporting the use of the two batch sizes will require evaluation although the more critical (b) (4) steps have the same scale in both. A DoE (b) (4) is included in 3.2.P.2.3.

The drug product specification is typical for an IR tablet:

<b>Table 2.3.P.5-1 Specifications for Brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg Tablets</b>		
<b>Test Item</b>	<b>Specifications</b>	<b>Test Method</b>
Description/Appearance	Conforms to Note	Visual
Identification (HPLC (b) (4))	Spectrum comparable to the reference standard	HPLC method (b) (4)
Impurities/Degradation products	(b) (4)	HPLC
Uniformity of dosage units Content uniformity <sup>a</sup>	Conforms to USP	HPLC
Dissolution	Q = (b) (4)% in 30 minutes	USP, Apparatus 2, 50 rpm, 900 mL of 0.05 mol/L acetate buffer
Assay	(b) (4)% of the label claim	HPLC
Microbial limit test <sup>b</sup>		
Microbial enumeration tests	TAMC: ≤ (b) (4) cfu/g, TYMC: ≤ (b) (4) cfu/g	USP <61> (b) (4)
Tests for specified microorganisms	<i>E. coli</i> : Absent	USP <62>

The demonstration batch analysis results appeared to meet specification. Impurity levels were all < (b) (4)%. The specified impurities (b) (4) were found after 18 months of room temperature storage – though just over the reporting threshold. More increases appeared to have occurred in the lower strengths in bottles and in the bulk tablets (at 12 months). (b) (4). A justification was provided. This will require evaluation. (b) (4)

The bulk tablets are packaged into HDPE bottles (b) (4) at various contract packaging sites in United States.

A bracketed stability protocol for the tablet strength is employed for the product in bottles –as per October 5, 2011 SPA. Full testing of the product (b) (4) was carried out (three batches of each strength). Data up to 18 months were provided in the original submission with additional data up to 24 months in the Aug 2014 amendment. The sponsor states that the data support a 36 month expiry period for each of the packaging configurations.

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

Executed batch records and method validation package were provided. Carton labels were provided. The dosage form is missing from the established name on the container labels. This will require correction. No comparability protocols are proposed.

**Biopharmaceutics Summary**

The efficacy, safety, and tolerability of brexpiprazole have been evaluated as an adjunctive therapy to antidepressant therapy (ADTs) for the treatment of adult patients with major depressive disorder (MDD) and for the treatment of adult patients with schizophrenia. For MDD, the recommended starting dose is 0.5-1 mg/day. Dose titration to 1 mg/day and up to the target dose of 2 mg/day should occur at intervals of up to 1 week based on the patient's clinical response and tolerability. The efficacy of brexpiprazole as an adjunctive therapy for MDD is considered by the Applicant to be established at doses of 2 mg/day and 3 mg/day. For schizophrenia, the recommended starting dose is 1 mg/day. The dose should be increased to 2 mg/day after day 4 and may subsequently be increased to 4 mg/day after day 7 based on the patient's clinical response and tolerability. The efficacy of brexpiprazole in the treatment of schizophrenia is considered by the Applicant to be established at doses of 2 mg/day and 4 mg/day.

A total of 28 clinical pharmacology and biopharmaceutics studies (one ongoing) have been performed as part of the product development program. The biopharmaceutics studies are:

- Study 332-10-243 – Bioequivalence (BE) between the commercial and P2 tablets
- Study 331-13-209 – Pivotal BE between the P3 commercial and clinical tablets.
- Study 331-13-245 – Dose strength equivalence of the LTSS/commercial tablets  
(*LTSS = long term stability study*)
- Study 331-01-241 – Absolute bioavailability
- Study 331-10-246 – Pivotal food effect study (4 mg)
- Study 331-07-201 – Pilot food effect study (2 mg)

As per the September 2013 MOU between Biopharmaceutics and the Office of Clinical Pharmacology, the Biopharmaceutics review will evaluate BE Studies 209 and 243. All other studies will be evaluated by the Office of Clinical Pharmacology. In addition to the BE studies, the proposed dissolution method and requested biowaivers will be reviewed.

Brexpiprazole is reported as a Biopharmaceutic Classification System (BCS) Class 2 drug substance, i.e., a low solubility, high permeability drug. Thus, tablet dissolution is an important risk factor for product safety and efficacy, and a dissolution method has been developed for routine product testing.

**Critical Review Issues**

1. The appropriateness of established process controls (e.g., dissolution) to assure product quality and bioavailability.
2. Bridging of formulation changes during development using in vitro (dissolution) or in vivo (bioequivalence) studies. With the BE studies, possible period carryover issues are noted

**Comments for Day 74-Letter**

1. Provide the PK parameter analysis datasets as SAS transport files for bioequivalence studies 209 and 243, preferably in stacked column format.

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

**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:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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>B. FACILITIES*</b>				
<b>* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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? <b>This question is not applicable for synthesized API.</b>			

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

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		Clarification was requested on the roles of the drug product sites. Adequate responses received.

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

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?			

**C. ENVIRONMENTAL ASSESMENT**

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

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

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
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	

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

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
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		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?			
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		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	x		DoE for formulation (b) (4) process. QTTP and CQAs identified.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	x		

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

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		'tablets' is missing from the established name

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>PARAMETER</b>	<b>YES</b>	<b>NO</b>	<b>COMMENT</b>
34.	Does the application contain dissolution data?	X		

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

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>PARAMETER</b>	<b>YES</b>	<b>NO</b>	<b>COMMENT</b>
35.	Is the dissolution test part of the DP specifications?	X		<p>There are three dissolution methods. All methods used the same dissolution testing parameters, but differ in the quantitation approach.</p> <p>Method (b) (4) (for 0.25- and 0.5-mg tablets)  Method (b) (4) (for 1- and 2-mg tablets),  Method (b) (4)</p> <p>- 900 mL, 0.05 mol/L acetate buffer, pH 4.3, USP 2 at 50 rpm</p> <p>The % of API released for the 3- and 4-mg tablets is measured by a UV absorbance method while HPLC method is applied for 0.25-, 0.5-, 1, and 2-mg tablets.</p> <p><b>Proposed Acceptance Criterion:</b> Q = (b) (4)% at 30 minutes.</p>
36.	Does the application contain the dissolution method development report?	X		Summarized in Section 3.2.P.2 Physicochemical and Biological Properties
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?	X		Biowaiver request for process changes.
39.	Does the application include an IVIVC model?		X	
40.	Is information such as BCS classification mentioned, and supportive data provided?	X		BCS II reported
41.	Is information on mixing the product with foods or liquids included?		X	

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

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b>A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>PARAMETER</b>	<b>YES</b>	<b>NO</b>	<b>COMMENT</b>
42.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		A total of 28 clinical pharmacology trials (one ongoing) have been performed as part of the brexpiprazole oral tablet development program.  PK data were also collected during clinical studies.
43.	Is any of the <i>in vivo</i> BA or BE under Biopharmaceutics review as per the Sept 2013 MOU)?	X		BE study for 3 mg. <i>Study 332-10-243</i> – BE between the commercial and P2 tablets <i>Study 331-13-209</i> – BE between the P3 commercial and clinical tablets. (BE criteria met based on Applicant's calculations)
44.	Is the to-be marketed formulation the same as used in clinical studies? If no, are bridging data submitted for review?	X		The to-be marketed and commercial formulations are the same, but there are differences in the manufacturing process.
45.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)?  b.) Is there information on the potential for alcohol-induced dose dumping?			Not applicable. The product is an IR formulation.

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

<b>B. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
46.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
47.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.
48.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	x		Provide the PK parameter analysis datasets as SAS transport files for bioequivalence studies 209 and 243, preferably in stacked column format.

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

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

*{See appended electronic signature page}*

*David Claffey*

CMC-Lead or CMC Senior Reviewer

Division

Office of New Drug Quality Assessment

*{See appended electronic signature page}*

*Minerva Hughes*

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Biopharmaceutics Team Leader or Designee

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*Olen Stephens*

Branch Chief or Designee

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Office of New Drug Quality Assessment

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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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DAVID J CLAFFEY  
09/22/2014

MINERVA HUGHES  
09/22/2014

ANGELICA DORANTES  
09/23/2014

OLEN M STEPHENS  
09/23/2014

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## INSPECTIONAL ASSIGNMENT (EMAIL TRANSMITTAL)

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**Date:** August 29, 2014

**To:** *International*  
Division of Medical Products and Tobacco Inspections  
Office of Regulatory Affairs

**Facility:** Otsuka Pharmaceuticals Co. Ltd.  
463-10, Kagasumo, Kawauchi-Chi  
Tokushima-Shi, Tokushima 771-0192, Japan  
**FEI No.: 3002809299**

**Drug Name  
(dosage form,  
strength/concentration):** Brexipiprazole Tablets  
0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg

**Profile Class:** TCM

**A/NDA No.:** NDA 205-422

**Team Leader** Thomas Wong  
CDER/OPS/ONDQA/DNDQA1  
[thomas.wong@fda.hhs.gov](mailto:thomas.wong@fda.hhs.gov), Tel: 301-796-1608

**Microbiology Reviewer (if  
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CDER has identified specific area(s) for inspectional focus for drug product manufacturing in connection with the ANDA 205-422. In accordance with the Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug substance by focusing on areas in which data is questionable; drug characteristics or sensitivities<sup>1</sup> indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

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<sup>1</sup> Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

**Summary of Product and Manufacturing Process:**

The drug product, Brexpiprazole tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg have been developed as (b) (4) immediate release tablets for use as adjunctive therapy in adults with MDD who had an inadequate/suboptimal response to antidepressant treatment and for monotherapy treatment of adults with schizophrenia.

All strengths of Brexpiprazole tablets are of the same shape, 6 mm in diameter and 93 mg of tablet weight. Brexpiprazole 0.25-mg tablets are light brown round (b) (4) tablets, debossed with “BRX” and “0.25” on one side; 0.5-mg tablets are light orange round (b) (4) tablets, debossed with “BRX” and “0.5” on one side; 1-mg tablets are light yellow round (b) (4) tablets, debossed with “BRX” and “1” on one side; 2-mg tablets are light green round (b) (4) tablets, debossed with “BRX” and “2” on one side; 3-mg tablets are light purple round (b) (4) tablet, debossed with “BRX” and “3” on one side; 4-mg tablets are white to off-white round (b) (4) tablet, debossed with “BRX” and “4” on one side. Brexpiprazole tablets are packaged in white, opaque HDPE bottles, induction heat-sealed (b) (4)

**Manufacturing Process:**

The manufacturing process is same for all strengths, 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets. To provide a flexible manufacturing to address market demands for 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets, a single batch (b) (4) may compose one lot of tablets (batch size-1), or two consecutive batches (b) (4) may be one lot (batch size-2), however, the manufacturing processes and equipment used are the same for both approaches. (b) (4)

(b) (4) The manufacturing process of Brexpiprazole tablets includes following steps:



(b) (4) Brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets (b) (4) consists of hypromellose, talc, titanium dioxide, and may include ferric oxide and/or ferrousferrous oxide for coloring same for all strengths of tablets. The quantitative composition of Brexpiprazole tablets is provided in Appendix 1.

The risks to the commercial manufacturing of brexpiprazole tablets were assessed during the manufacturing process development. The factors potentially affecting the commercial manufacture were assessed collectively and by unit operation to assess whether any factor was critical. Based on the comprehensive quality risk assessment, design of experiments and production experience gained from the clinical and development batches, and optimization study, the firm concluded that the manufacturing process development mitigated potential risk of routine production and the established commercial manufacturing process for this product is robust. Therefore it is considered that the manufacturing process of Brexpiprazole tablets has no critical steps.

The following table shows the updated risk assessment in the proposed commercial production:

Factors	Potential CQA				
	Description	Assay	Content Uniformity	Dissolution	Impurity/Degradation Products
Drug substance	Low	Low	Low	Risk mitigation	Low
Excipients	Low	Low	Low	Risk mitigation	Low
(b) (4)	NA	Low	NA	NA	NA
	NA	Low	Low	Risk mitigation	Low
	NA	Low	Low	Low	Low
	NA	NA	Low	Low	NA
	NA	Low	Low	NA	NA
	NA	Low	Low	Risk mitigation	NA
	Low	Low	Low	Risk mitigation	Low
	Low	NA	NA	NA	Low
Inspection	Low	NA	NA	NA	NA
Packaging	NA	NA	NA	NA	Low

NA = not applicable

To justify the manufacturing process for batch size-2, eighteen (18) process justification study batches of 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets were manufactured at the proposed commercial

manufacturing site using the batch formulas and manufacturing processes as given in the process flow chart. These process justification batches are given in the following table:

**Process Justification on 0.25- to 4-mg Tablets**

<b>Table 3.2.P.3.5-1 Brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg Tablets Used for Process Justification Studies (Batch size-2)</b>				
<b>Brexpiprazole Tablets</b>	<b>Batch scale</b>	<b>Representative Batch Number From Each Production Campaign (Manufacturing site : Tokushima Factory)</b>		
0.25-mg Tablets	(b) (4)	11G74A0025 <sup>a</sup>	11G75A0025 <sup>a</sup>	11G76A0025 <sup>a</sup>
0.5-mg Tablets		10J91A0050A <sup>a</sup>	10J91A0050B <sup>a</sup>	10J91A0050C <sup>a</sup>
1-mg Tablets		10J96A001A <sup>a</sup>	10J96A001B <sup>a</sup>	10J96A001C <sup>a</sup>
2-mg Tablets		10K70A002A <sup>a</sup>	10K70A002B <sup>a</sup>	10K70A002C <sup>a</sup>
3-mg Tablets		10K74A003A <sup>a</sup>	10K74A003B <sup>a</sup>	10K74A003C <sup>a</sup>
4-mg Tablets		11G77A004 <sup>a</sup>	11G80A004 <sup>a</sup>	11G81A004 <sup>a</sup>

<sup>a</sup> 3 consecutive batches for each strength is abbreviated as Batch A, Batch B and Batch C, respectively in this section.

The firm provided test data (b) (4) for these batches. The content uniformity data for batches manufactured for 0.25 mg and 4 mg tablets were provided. All the test data provided in the application by the firm are for batch size -2 (two consecutive batches (b) (4) for one lot of tablets).

*Note: Manufacturing flow chart and tables provided in this memo are taken from the application.*

- Quantitative Composition of Brexpiprazole Tablets -----Appendix I
- Release Specifications for Brexpiprazole Tablets -----Appendix II
- Blend Uniformity (b) (4) (Batch Size 2) -----Appendix III
- Physicochemical Test Results for (b) (4) Brexpiprazole Tablets-----Appendix IV

**The following is a brief explanation of product or process specific issues that should receive follow-up during the inspection.**

**I. Chemistry Review**

The chemistry reviewer, Thomas Wong indicated that there is no GMP/Compliance issue for the manufacturing of drug product. However, as these tablets are low strength tablets, blend and content uniformity is a concern. The following comments were provided:

- Evaluate the blend uniformity data

[OC Note: Refer to III. a (iv) for inspectional coverage]

- The firm provided content uniformity data for two tablet strengths, Brexpiprazole 0.25 mg tablets and 4 mg tablets. Please see whether stratified sampling method was used for the content uniformity and their results.

[OC Note: Refer to **III. b (ii)** for inspectional coverage]

## **II. Microbiology Review**

A microbiologist did not provide any comments for microbiological issues.

## **III. Manufacturing**



(b) (4)

#### **IV. Quality Control / Quality Assurance**

##### **a. Quality System**

- i. Determine if any OOS results or deviations or rejections have occurred during development or production of submission batches, and report on adequacy of investigations and corrective actions.
- ii. Determine if all laboratory test instruments are adequate for their intended use (qualified). Review the analytical methods for release and stability and determine if the firm's raw data demonstrates that they are validated and stability indicating.

##### **c. Stability**

- i. Review the firm's exhibit batch stability data and any other stability data generated by the firm for this product to determine if the testing was conducted in accordance with

the submitted stability protocol, whether stability samples were stored under appropriate storage conditions, whether the testing was conducted appropriately, and whether the stability test results meet all specifications. Include a review of pertinent raw test data. Verify whether the stability data reported in the ANDA is accurate and complete.

**d. Raw Materials**

- i. Determine if there were any OOS results for any incoming raw materials used in the formulation. If so, review OOS investigations, and determine what corrective/preventive actions were implemented to address these OOS results.
- ii. Select one or more key significant materials in the formulation (e.g., Brexpiprazole) for audit and determine if the firm has qualified all suppliers for the raw material. Also, evaluate if incoming raw material quality control testing is sufficient for the raw material(s) selected for audit.

**e. Validation**

- i. Review the process validation plan (i.e., process performance qualification) which specifies the procedures (and tests) to be conducted and the data to be collected, if available. Determine if the plan includes an evaluation of the suitability of materials and an evaluation of consistent adherence to pre-established process parameters and quality attributes.
- ii. Determine if the firm has integrated this drug into its (b) (4) validation approach for multi-use equipment and evaluate the (b) (4) validation program.

**f. Distribution Supply Chain**

- i. Determine if the firm's quality system ensures that its Quality Control Unit (QCU) approves all suppliers and knows the identity of the manufacturer (not only the distributor) of all of its ingredients. All ingredients need to be received from manufacturing sources that are approved and qualified by QCU, and from a reliable supply chain.

A pre-inspection briefing may be scheduled if additional clarification or background is needed. Should you have questions prior to, during or post inspection, please contact the CDER officials identified above.

Please report your findings regarding these issues in the Establishment Inspection Report (EIR) under the heading, "ADDITIONAL INFORMATION" with the subheading, "Follow-up to CDER PAI Questions."

**THIS ASSIGNMENT IS CONFIDENTIAL FDA CORRESPONDENCE**

cc:

Mahesh Ramanadham, Acting Branch Chief

Juandria Williams, Acting Team Leader

Steve Lynn, Rick Friedman, Carmelo Rosa, Elizabeth Philpy, Montemurro, Laska, Chasey, Mueller,  
Lead investigator

CDER-KTM@fda.hhs.gov

OC Doc. No.: KTM-2014-017

APPENDIX I

Quantitative Composition of Brexpiprazole Tablets

Component	Quality Standard	Function	0.25-mg		0.5-mg		1-mg		2-mg		3-mg		4-mg	
			mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)	mg	(b) (4)
Brexpiprazole	In-house	Active ingredient	0.25		0.5		1.0		2.0		3.0		4.0	
Lactose monohydrate <sup>b</sup>	NF													(b) (4)
Corn starch	NF													
Microcrystalline cellulose	NF													
Low-substituted hydroxypropyl cellulose	NF													
Hydroxypropyl cellulose <sup>c</sup>	NF													
Magnesium stearate <sup>d</sup>	NF													(b) (4)
Total tablet weight (mg)			93.0		93.0		93.0		93.0		93.0		93.0	
Tablet description (Tablet weight / diameter : 93 mg / 6 mm)			Light brown, round, shallow convex, beveled-edged tablet, debossed with BRX and 0.25 on one side		Light orange, round, shallow convex, beveled-edged tablet, debossed with BRX and 0.5 on one side		Light yellow, round, shallow convex, beveled-edged tablet, debossed with BRX and 1 on one side		Light green, round, shallow convex, beveled-edged tablet, debossed with BRX and 2 on one side		Light purple, round, shallow convex, beveled-edged tablet, debossed with BRX and 3 on one side		White, round, shallow convex, beveled-edged tablet, debossed with BRX and 4 on one side	

NF = National Formulary; USP = US Pharmacopeia; qs = quantity sufficient;

(b) (4)

APPENDIX II

Release Specifications for Brexpiprazole Tablets

Table 3.2.P.5.1-1 Specifications for Brexpiprazole 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg Tablets		
Test Item	Specifications	Test Method
Description/Appearance	Conforms to Note	Visual
Identification (HPLC: (b) (4))	Spectrum comparable to the reference standard	HPLC method (b) (4)
Impurities/Degradation products	(b) (4)	HPLC
Uniformity of dosage units Content uniformity <sup>a</sup>	Conforms to USP	HPLC
Dissolution	Q = (b) (4) in 30 minutes	USP, Apparatus 2, 50 rpm, 900 mL of 0.05 mol/L acetate buffer
Assay	(b) (4) of the label claim	HPLC
Microbial limit test <sup>b</sup>		
Microbial enumeration tests	TAMC: (b) (4) cfu/g, TYMC: (b) (4) cfu/g	USP <61>, Pour-plate method
Tests for specified microorganisms	<i>E. coli</i> : Absent	USP <62>

Note: 0.25-mg tablets: light brown round film coated tablets, debossed with “BRX” and “0.25” on one side; 0.5-mg tablets: light orange round film coated tablets, debossed with “BRX ” and “0.5” on one side; 1-mg tablets: light yellow round film coated tablets, debossed with “BRX ” and “1” on one side; 2-mg tablets: light green round film coated tablets, debossed with “BRX ” and “2” on one side; 3-mg tablets: light purple round film coated tablet, debossed with “BRX” and “3” on one side; 4-mg tablets: white to off-white round film coated tablet, debossed with “BRX” and “4” on one side

(b) (4) TAMC = total aerobic microbial count; TYMC = total combined yeasts and moulds count

<sup>a</sup> performed only at release

<sup>b</sup> tested for the first three commercial-scale batches and every tenth batch or one lot every year thereafter

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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VIPULCHANDRA N DHOLAKIA  
08/29/2014

JUANDRIA WILLIAMS  
08/29/2014