CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205836Orig1s000
205837Orig1s000
205838Orig1s000

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: December 16, 2015

From: Martha R. Heimann, Ph.D., CMC Lead, OPQ/ONDP and ATL for NDA 205836

To: NDA 205836

Subject: Approval Recommendation for NDA 205836, Briviact (brivaracetam) Tablets

This memorandum is an addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 205836 dated August 10, 2015. At the time the original review was entered into Panorama, the final recommendation was pending completion of inspections for the UCB Pharma Belgium site that manufactures the bulk drug substance and brivaracetam tablets and for a contract testing facility, (b) (4) There were no other outstanding quality issues.

The (b) (4) facility was inspected on (b) (4) through (b) (4). The outcome of the inspection was no action indicated (NAI) and a Form 483 was not issued.

A preapproval inspection was performed at the UCB site from September 3 through September 11, 2015. The Office of Process and Facilities (OPF) Facility reviewer for this application, Ebern Dobbin, was a member of the inspection team. The outcome of the inspection was no action indicated (NAI) and a Form 483 was not issued.

Per the final facility review addendum (E. Dobbin, December 11, 2015), all manufacturing facilities are considered acceptable. The overall manufacturing inspection recommendation is for Approval of the application. Based on the Facility recommendation, and the previous approval recommendations from the other members of the review team, OPQ recommends approval of NDA 205836.

Martha R. Heimann -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
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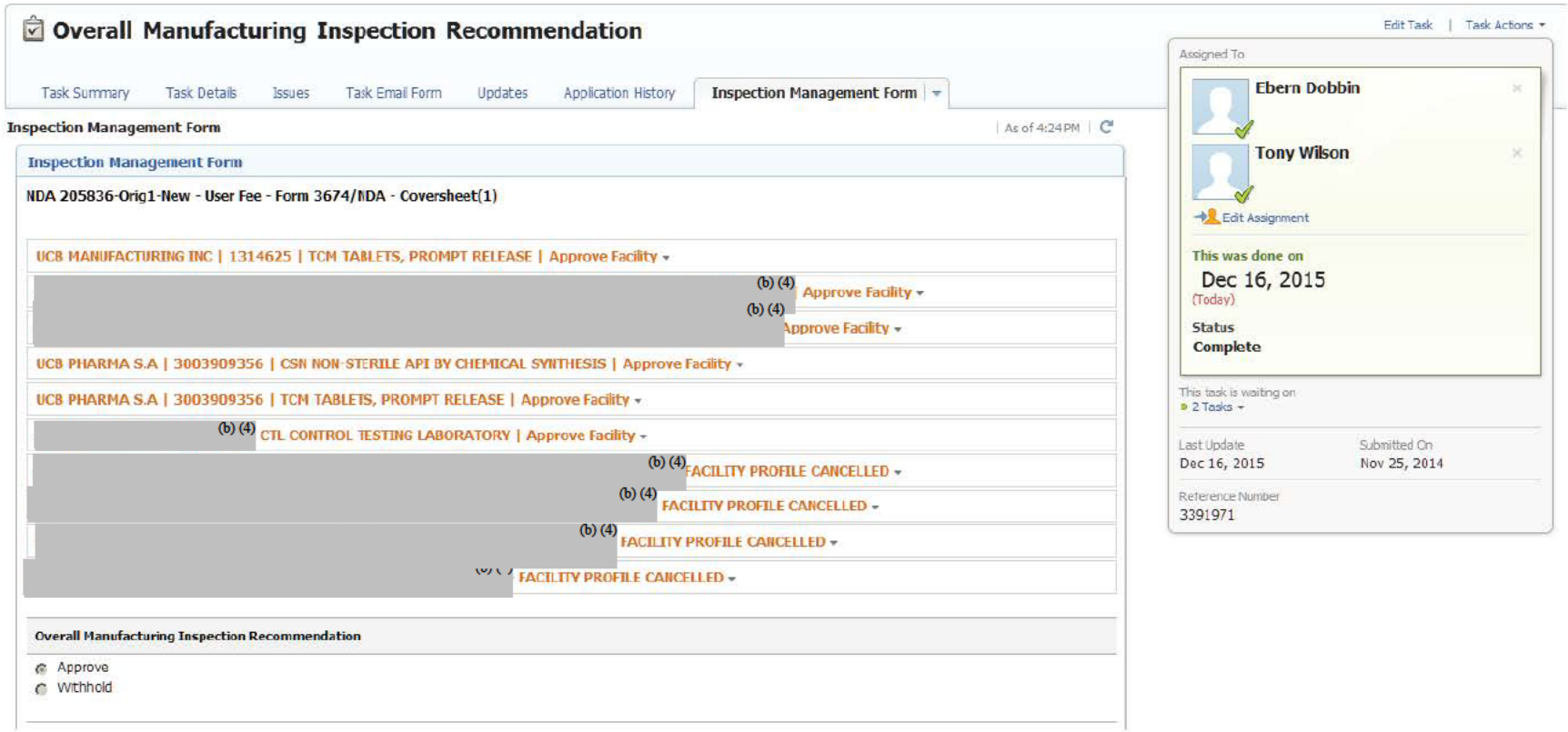
Overall Manufacturing Inspection Recommendation
Edit Task | Task Actions
Task Summary
Task Details
Issues
Task Email Form
Updates
Application History
Inspection Management Form
Inspection Management Form
As of 4:24PM
Inspection Management Form
NDA 205836-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)
UCB MANUFACTURING INC | 1314625 | TCM TABLETS, PROMPT RELEASE | Approve Facility
(b) (4) Approve Facility
(b) (4) Approve Facility
UCB PHARMA S.A | 3003909356 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
UCB PHARMA S.A | 3003909356 | TCM TABLETS, PROMPT RELEASE | Approve Facility
(b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
FACILITY PROFILE CANCELLED
Overall Manufacturing Inspection Recommendation
Approve
Withhold
Assigned To
Ebern Dobbin
Tony Wilson
Edit Assignment
This was done on
Dec 16, 2015
(Today)
Status
Complete
This task is waiting on
2 Tasks
Last Update
Dec 16, 2015
Submitted On
Nov 25, 2014
Reference Number
3391971

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: December 16, 2015

From: Martha R. Heimann, Ph.D., CMC Lead, OPQ/ONDP and ATL for NDA 205837

To: NDA 205837

Subject: Approval Recommendation for NDA 205837, Briviact (brivaracetam) Injection

This memorandum is an addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 205837 dated August 10, 2015. At the time the original review was entered into Panorama, the final recommendation was pending completion of inspection for the UCB Pharma Belgium that manufactures the bulk drug substance and brivaracetam injection. There were no other outstanding quality issues.

A preapproval inspection was performed at the UCB site on September 3 through September 11, 2015. The Office of Process and Facilities (OPF) Facility reviewer for this application, Ebern Dobbin, was a member of the inspection team. The outcome of the inspection was no action indicated (NAI) and a Form 483 was not issued.

Per the final facility review addendum (E. Dobbin, December 11, 2015), all manufacturing facilities are considered acceptable. The overall manufacturing inspection recommendation is for Approval of the application. Based on the Facility recommendation, and the previous approval recommendations from the other members of the review team, OPQ recommends approval of NDA 205837.

Martha R. Heimann -S

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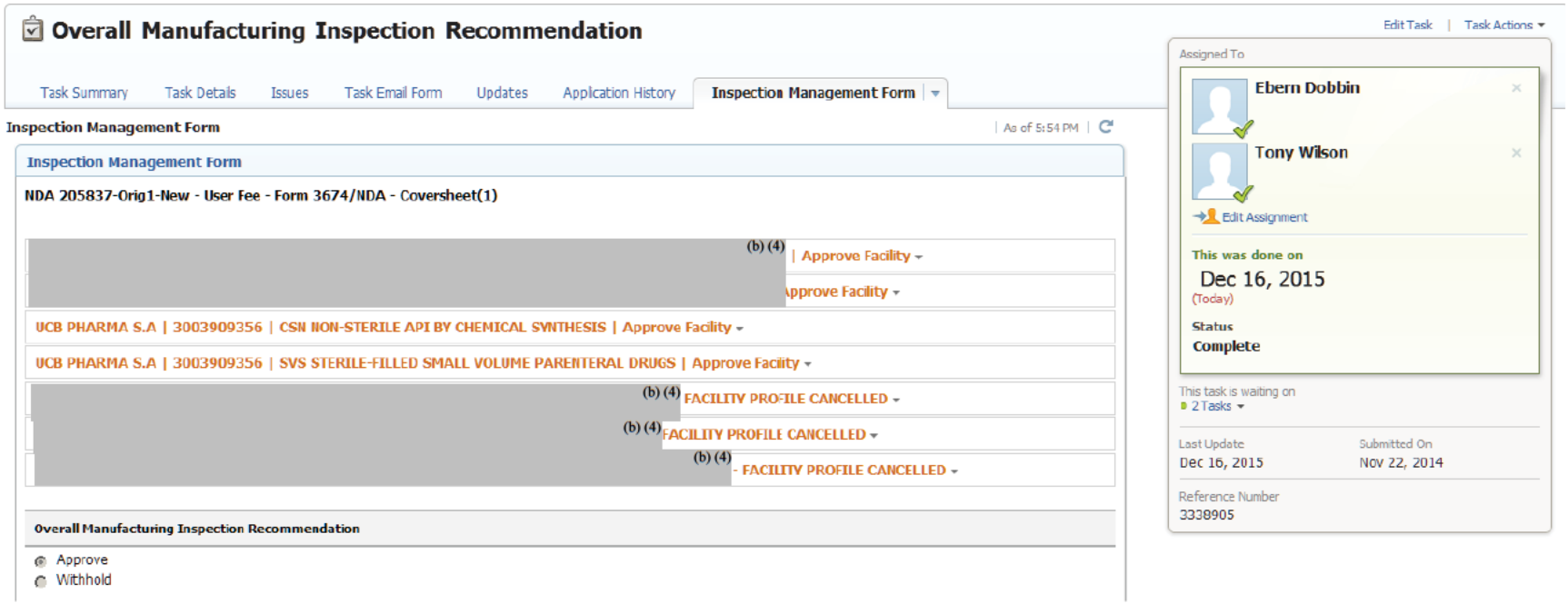
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
Date: 2015.12.16 18:20:12 -05'00'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As of 5:54 PM
Inspection Management Form
NDA 205837-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)
(b) (4) | Approve Facility
Approve Facility
UCB PHARMA S.A | 3003909356 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
UCB PHARMA S.A | 3003909356 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) - FACILITY PROFILE CANCELLED
Overall Manufacturing Inspection Recommendation
Approve
Withhold
Assigned To
Ebern Dobbin
Tony Wilson
Edit Assignment
This was done on
Dec 16, 2015
(Today)
Status
Complete
This task is waiting on
2 Tasks
Last Update
Dec 16, 2015
Submitted On
Nov 22, 2014
Reference Number
3338905

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

Date: December 16, 2015

From: Martha R. Heimann, Ph.D., CMC Lead, OPQ/ONDP and ATL for NDA 205838

To: NDA 205838

Subject: Approval Recommendation for NDA 205838, Briviact (brivaracetam) Oral Solution

This memorandum is an addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 205838 dated August 10, 2015. At the time the original review was entered into Panorama, the final recommendation was pending completion of inspection for the UCB Pharma Belgium that manufactures the bulk drug substance. There were no other outstanding quality issues.

A preapproval inspection was performed at the UCB site from September 3 through September 11, 2015. The Office of Process and Facilities (OPF) Facility reviewer for this application, Ebern Dobbin, was a member of the inspection team. The outcome of the inspection was no action indicated (NAI) and a Form 483 was not issued.

Per the final facility review addendum (E. Dobbin, December 11, 2015), all manufacturing facilities are considered acceptable. The overall manufacturing inspection recommendation is for Approval of the application. Based on the Facility recommendation, and the previous approval recommendations from the other members of the review team, OPQ recommends approval of NDA 205838.

Martha R. Heimann -S

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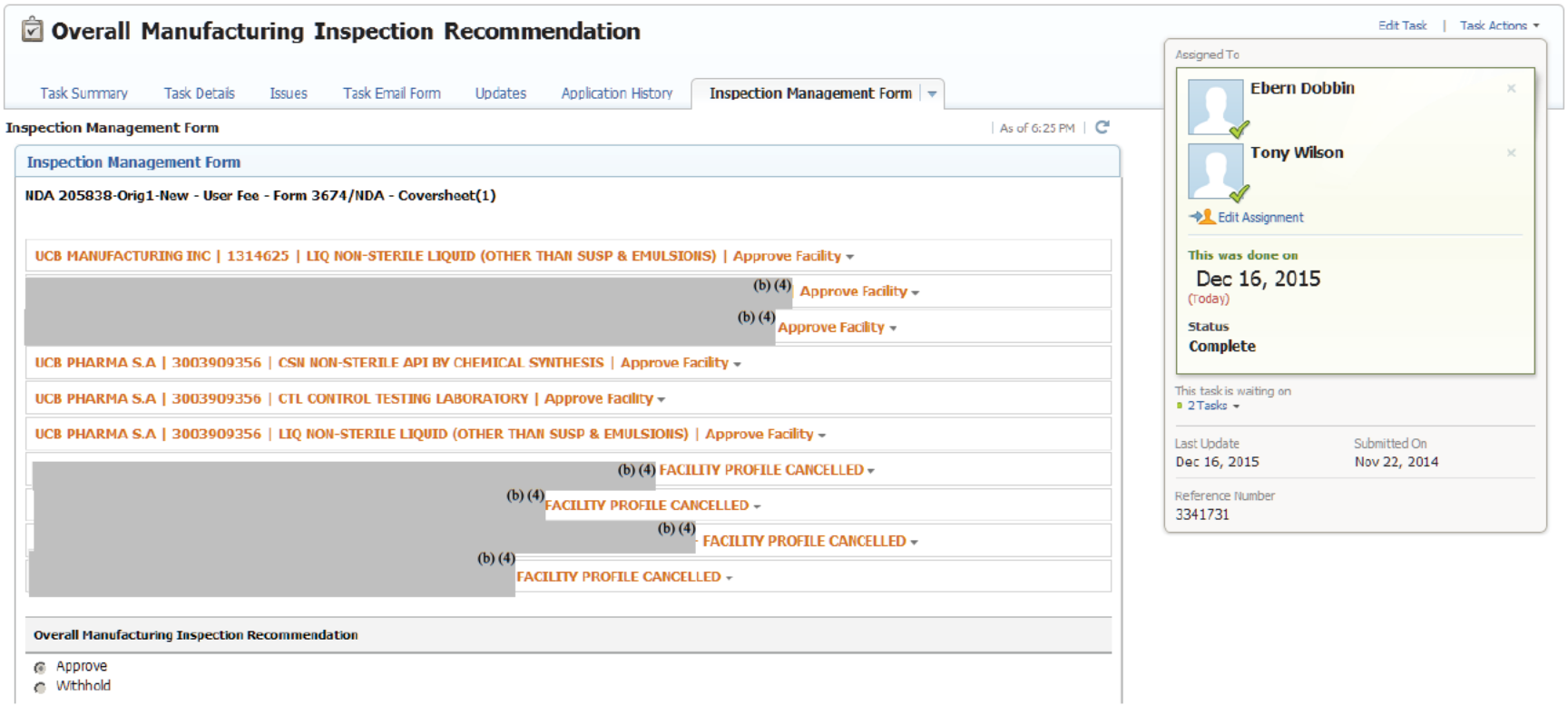
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Updates
Application History
Inspection Management Form
Inspection Management Form
As of 6:25 PM
Inspection Management Form
NDA 205838-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)
UCB MANUFACTURING INC | 1314625 | LIQ NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS) | Approve Facility
(b) (4) Approve Facility
(b) (4) Approve Facility
UCB PHARMA S.A | 3003909356 | CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility
UCB PHARMA S.A | 3003909356 | CTL CONTROL TESTING LABORATORY | Approve Facility
UCB PHARMA S.A | 3003909356 | LIQ NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS) | Approve Facility
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
(b) (4) FACILITY PROFILE CANCELLED
Overall Manufacturing Inspection Recommendation
Approve
Withhold
Assigned To
Ebern Dobbin
Tony Wilson
Edit Assignment
This was done on
Dec 16, 2015
(Today)
Status
Complete
This task is waiting on
2 Tasks
Last Update
Dec 16, 2015
Submitted On
Nov 22, 2014
Reference Number
3341731

ASSESSMENT OF THE FACILITIES

This is an addendum to the Overall Quality Assessment for NDA 205836 that was filed in Panorama review platform August 10, 2015. This addendum provides an updated and final assessment of the Drug Substance Manufacturing facility (see: ***Question #31, Overall Quality Assessment***) and the final assessment of the Drug Product Manufacturing facility (see: ***Question #32, Overall Quality Assessment***) as well as the Overall Facility Review Assessment.

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		CSN	(b) (4)	*NME	GMP Inspection (b) (4) 2 item 483,	Acceptable
		CSN		*NME	Surveillance Inspection Conducted (b) (4) No FDA 483	Acceptable
UCB Pharma Belgium	3003909356	CSN		*NME (b) (4)	PAI & GMP coverage performed 9/3-9/11/2015; NAI	Acceptable

			(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance			

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	(b) (4)	Low	Low	High	**High**
		CSN		Low	Low	High	**High**
UCB Pharma Belgium	**30039093 56**	**CSN**	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	Low	Low	High	**High**

(b) (4)

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2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
UCB Pharma Belgium	3003909356	TCM	*Manufacte, *Package, *Release testing, *Stability testing	(b) (4) tablet, (b) (4) *NME	The PAI inspection was performed from 9/3-9/11/2015.	Acceptable
(b) (4)		TCM	*Packaging,	*NME	No FDA 483 observations for the PAI/Surveillance inspection in (b) (4)	Acceptable
		CTL	*Release testing, *Stability testing	*NME	No FDA 483 observations	Acceptable
		CTL	(b) (4) *Stability testing	Process *NME	*PAI and GMP (b) (4) *No 483 issued *Stability testing (b) (4) Profile CTL	Acceptable

Reviewer's Assessment:

Initial Facility Risk Assessment for the firms involved in drug product manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
UCB Pharma	3003909356	TCM	*Manufacture, *Packaging, *Release testing, *Stability testing	Low	Medium	High	High
(b) (4)		TCM	*Packaging	Low	Low	High	High
		CTL	*Release testing, *Stability testing	Low	Low	High	High
		CTL	*Release testing, *Stability testing	Low	Low	High	High

UCB Pharm Belgium (FEI 3003909356) responsibilities are to manufacture API, and solid dosage (TCM profile) drug product manufacturing and packaging, release testing and stability testing.

Risks and Critical Steps

(b) (4)

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(b) (4)

The firm appeared to be operation within compliance to their written procedures. There were no observations and the outcome of the inspection was NAI.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant outstanding manufacturing risks that will affect this application.

A pre-approval inspection (PAI) was performed at **UCB Pharma (FEI 3003909356)** from August 31 thru September 2, 2015. (b) (4) were covered during the inspection. Profiles CSN for active ingredient and TCM for tablets were covered. There were no issues or FDA 483 observations. The firm appeared to be in a state of control. (b) (4) All process validation had been completed and was reviewed during the inspection. Overall the firm appeared to be in a state of control. This firm receives an **ACCEPTABLE** recommendation.

A combination PAI and surveillance inspection was performed for (b) (4) to cover the contract laboratory testing operations. There were no issues or concerns at either site. The laboratory was contracted to perform stability testing (b) (4)

(b) (4)

. The firm appears to be operating within a state of control and within FDA compliance in addition to following its procedures. This firm receives an **ACCEPTABLE** recommendation.

Ebern Dobbin
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Ebern Dobbin -S

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Date: 2015.12.14 13:30:52 -05'00'

Supervisor Comments and Concurrence:

I concur with this acceptable recommendation.

Christina Capacci-Daniel, PhD – Dec 11, 2015
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Christina A. Capacci-daniel -S

Digitally signed by Christina A. Capacci-daniel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001273747, cn=Christina A. Capacci-daniel -S
Date: 2015.12.14 13:41:32 -05'00'

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE FACILITIES

This is an addendum to the Overall Quality Assessment for NDA 205837 that was filed in Panorama review platform August 10, 2015. This addendum provides an updated and final assessment of the Drug Substance Manufacturing facility (see: ***Question #30, Overall Quality Assessment***) and the final assessment of the Drug Product Manufacturing facility (see: ***Question #31, Overall Quality Assessment***) as well as the Overall Facility Review Assessment.

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Applicant's Response:

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
	(b) (4)	CSN	(b) (4)	* NME	GMP Inspection (b) (4) 2 item 483,	Acceptable
		CSN		*NME	Surveillance Inspection Conducted (b) (4) No FDA 483	Acceptable

UCB Pharma Belgium	3003909356	CSN	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	*NME (b) (4)	PAI & GMP coverage performed 9/3-9/11/2015; NAI	Acceptable

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	(b) (4)	Low	Low	High	High
		CSN		Low	Low	High	High
UCB Pharma Belgium	**3003909356**	**CSN**	*Release testing of	Low	Low	High	High

			drug substance, *Packaging of drug substance, *Stability testing of drug substance				

(b) (4)

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(b) (4)

There were no issues or observed. The firm appears to be operating within compliance and following their procedures. Full coverage of API manufacturing and testing was performed and the CSN profile was updated. The firm appears to be operating in a state of compliance and has been given a cGMP status of **NAI** and PAI recommendation of: **ACCEPTABLE** for responsibilities specified in the application.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

QUALITY REVIEW

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
UCB Pharma Belgium	3003909356	(b) (4)	Manufacture, packaging, release testing, stability testing	*NME	PAI coverage for (b) (4) profile inspection completed 9/1-9/11/2015 and was NAI	Acceptable

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug product manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
UCB Pharma Belgium	3003909356	(b) (4)	*Manufacturing *Packaging, *Release testing *Stability testing	Low	Low	High	High

UCB Pharm Belgium (FEI 3003909356), performs the sterile drug product (b) (4) manufacturing, packaging, release testing and stability testing.

Risks

(b) (4)

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(b) (4)

The firm appears to be operating in a state of compliance and has been given a cGMP status of **NAI** and a classification: ACCEPTABLE. The firm's history would suggest that they are successful in their product and process development and that they are compliant to GMP regulations. While this product is an NME, the firm has a successful history of manufacturing sterile drug products.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:
All facilities associated with this application have an **ACCEPTABLE** cGMP status.

Following a review of the application and inspectional documents, there are no significant outstanding manufacturing risks that will affect this application. Pre-approval (PAI) and GMP inspection coverage was performed at **UCB Pharma (FEI 3003909356)** from September 3 thru September 11, 2015. (b) (4) were covered during the inspection. Profiles CSN for active ingredient and drug product manufacturing were covered. There were no issues or FDA 483 observations. The firm's good history suggests they are successful in process and product development and they are also compliant to GMP regulations. The firm appears to be in a state of control. (b) (4) The firm appears to be operating within a state of compliance. There were no issues of concern to be addressed. The cGMP status is classified as NAI and the site was given the recommendation: **ACCEPTABLE**

(b) (4) profile was not covered during the most recent inspection because (b) (4) product specific inspections for

QUALITY REVIEW

(b) (4) profiles were performed in (b) (4). There were no major issues and the cGMP status of the last inspection covering (b) (4) profile was VAI.

This firm, and all other firms in this application, receive an **ACCEPTABLE** recommendation.

Ebern Dobbin
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Ebern Dobbin -S

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Date: 2015.12.14 13:29:59 -05'00'

Supervisor Comments and Concurrence:

I concur with this acceptable recommendation.

Christina Capacci-Daniel, PhD – Dec 11, 2015
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Christina A. Capacci-daniel -S

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Date: 2015.12.14 13:43:07 -05'00'

ASSESSMENT OF THE FACILITIES

This is an addendum to the Overall Quality Assessment for NDA 205838 that was filed in Panorama review platform August 10, 2015. This addendum provides an updated and final assessment of the Drug Substance Manufacturing facility (see: ***Question #30, Overall Quality Assessment***) and the final assessment of the Drug Product Manufacturing facility (see: ***Question #31, Overall Quality Assessment***) as well as the Overall Facility Review Assessment.

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Applicant's Response:

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		CSN	(b) (4)	* NME,	GMP Inspection (b) (4), 2 item 483	Acceptable
		CSN		*NME	Surveillance Inspection Conducted (b) (4), No FDA 483	Acceptable

UCB Pharma Belgium	3003909356	CSN	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	*NME (b) (4)	PAI & GMP coverage performed 9/1-9/12/2015; NAI	Acceptable

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	(b) (4)	Low	Low	High	High
		CSN		Low	Low	High	High

UCB Pharma Belgium	**30039093 56**	**CSN**	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	Low	Low	High	High

(b) (4)

Risks and Critical Parameters

(b) (4)

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(b) (4)

There were no issues or observed. The firm appears to be operating within compliance and following their procedures. Full coverage of API manufacturing and testing was performed and the CSN profile was updated. The firm appears to be operating in a state of compliance and has been given a cGMP status of **NAI** and PAI recommendation of: **ACCEPTABLE** for responsibilities specified in the application.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

Facility Name	FEI Number	Profile Code	Responsibilities	Initial Risks Identified	Current Status	Final Recommendation

[redacted] (b) (4)				NME	The PAI inspection was performed from [redacted] (b) (4)	N/A; This facility has been removed from the 356H at the present time since it will not be performing this function in the near future.
UCB Pharma Belgium	3003909356	CTL	Release testing, stability testing	NME	The PAI inspection was performed from 9/3-9/11/2015. NAI	ACCEPTABLE
[redacted] (b) (4)		LIQ	Manufacturing, Packaging, Release testing, stability testing	Low risk based on GMP history of the facility, site history with profile, (b) (4) [redacted] (b) (4) history, in addition to this being a non-sterile drug product	No FDA 483 Issued	ACCEPTABLE

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug product manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
[redacted] (b) (4)				Low	Low	High	High
UCB Pharma Belgium	**3003909356**	**CTL**	*Release testing *Stability testing	Low	Low	High	High
[redacted] (b) (4)		**LIQ**	*Manufacturing *Packaging, *Release testing *Stability testing	Low	Low	High	High

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inspection for NDA 205838. The investigators verified the completion and implementation of corrective and preventive actions from the prior inspection. There were no deficiencies found during the current inspection, therefore no FDA 483 was issued. The final classification for this inspection was NAI.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:
All facilities associated with this application are current in their GMP status and each has been recommended as: **ACCEPTABLE**

(b) (4)

(b) (4) received a pre-approval and surveillance inspection in (b) (4). The overall status of the inspection is NAI and the district gave recommendation for the approval of NDA 205838 for the assigned responsibilities at that site. This site is **ACCEPTABLE**.

Ebern Dobbin
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Ebern Dobbin -S
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Date: 2015.12.14 13:29:05 -05'00'

Supervisor Comments and Concurrence:

I concur with this acceptable recommendation.

Christina Capacci-Daniel, PhD – Dec 11, 2015
Acting QAL / Consumer Safety Officer, OPQ/OPF/DIA/IABII

Christina A. Capacci-daniel -S
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Note: additional reviewers can be added, as appropriate

NDA 205836
Review # 1

Drug Name/Dosage Form	Brivaracetam Tablets
Strength	10 mg, 25 mg, 50 mg, 75 mg, and 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	UCB Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Quality Amendment	12/22/14
Quality Amendment	1/12/15
Quality Amendment	3/10/15
Quality Amendment	4/24/15
Quality Amendment	5/20/15
Quality Amendment	6/17/15
Quality Amendment	7/13/15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell	Division of New Drug API
Drug Product	Andrei Ponta	Division of New Drug Products I
Process	Bogdan Kurtyka	Division of Process Assessment I
Microbiology	Denise Miller	DMA/Branch II
Facility	Ebern Dobbin	Division of Inspectional Assessment
Biopharmaceutics	Okpo Eradiri	Division of Biopharmaceutics
Project/Business Process Manager	Dahlia A. Woody	RBPM Division I
Application Technical Lead	Martha Heimann	Division of New Drug Products I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Table of Contents

Quality Review Data Sheet

LEGAL BASIS FOR SUBMISSION: 505(b)(1)

1. RELATED/SUPPORTING DOCUMENTS:

- **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A		Enough data in NDA
	Type III			Adequate[2]	N/A	
	Type III			Adequate[2]	N/A	
	Type III			Adequate[2]	N/A	
	Type IV			N/A		Enough data in NDA

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[2] Previously reviewed with no new information

A. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70205	Solid oral formulations for epilepsy
IND	(b) (4)	
IND	103908	Development of iv formulation
IND	110606	Development of an oral solution in pediatric epilepsy
NDA	205837	IV formulation
NDA	205838	Oral solution

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation is pending completion of an inspection at the drug substance manufacturing facility. The inspection is scheduled for completion prior to the GRMP goal date for facility inspections. At that time, an addendum to this review containing the final recommendation will be entered into Panorama. There are no other outstanding issues that would preclude an approval recommendation.

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

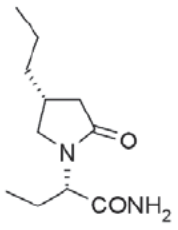
There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

II. Summary of Quality Assessments

A. Drug Substance Quality Summary for Brivaracetam

Brivaracetam [chemical name: (2S)-2-[(4R)-2-oxo-4-propyl-tetrahydro-1H-pyrrol-1-yl]butanamide] is a new chemical entity developed by the applicant, UCB Inc., for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older. The chemical structure of brivaracetam (shown below) is similar to levetiracetam, an approved, widely used, antiepileptic drug marketed by the applicant under the trade name Keppra®. The only difference between brivaracetam and levetiracetam is that levetiracetam lacks the propyl side chain at the 4-position of the lactam ring.

Chemical Structure of Brivaracetam



Brivaracetam is a neutral, small molecule that is highly soluble in aqueous media at 37°C across the physiologically relevant pH range [approximately 0.85 grams/mL at pH 1.2, pH 4.,5 and pH 7.4]. It is also highly permeable. In a radioactive mass balance study urinary excretion reached 96.8% of the brivaracetam dose.

(b) (4)

Brivaracetam is manufactured (b) (4)

Brivaracetam for parenteral use (NDA 205837) is manufactured (b) (4)

Brivaracetam drug substance is packaged in (b) (4) that comply with FDA requirements for food contact application. (b) (4)

The stability data provided in the application support a re-test period of at least (b) (4) months for oral grade brivaracetam, and at least (b) (4) months for the injectable grade material (b) (4). The re-test period for injectable grade brivaracetam may be extended based on additional data from ongoing studies.

B. Drug Product Quality Summary for Brivaracetam Tablets

Brivaracetam tablets are conventional, immediate release, film-coated, 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets. The recommended Brivaracetam starting dose is 50 mg twice daily. Based on individual patient response, the dose may be adjusted

between 25 mg twice daily to 100 mg twice daily. The applicant intends to market 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg strength tablets to allow for dose adjustments; the 10 mg tablet allows for intermediate dose adjustment between the higher strengths. The proposed commercial tablets are differentiated by size, shape, color, and debossed code on one face of the tablet.

- 10 mg tablet - White to off-white round film-coated tablet debossed with "u10"
- 25 mg tablet - Grey oval film-coated tablet debossed with "u25"
- 50 mg tablet - Yellow oval film-coated tablet debossed with "u50"
- 75 mg tablet - Purple oval film-coated tablet debossed with "u75"
- 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100"

The Brivaracetam tablet (b) (4) is composed of the drug substance and the following excipients: croscarmellose sodium, lactose monohydrate, betadex, anhydrous lactose, and magnesium stearate. The tablets are coated with (b) (4) film-coating agents containing polyvinyl alcohol, talc, PEG 3350, titanium dioxide, and iron oxide. The desired colors are achieved by varying the levels of red, yellow and black iron oxide. The film-coat for the 10 mg tablet does not contain iron oxide.

Brivaracetam tablets are manufactured using conventional processes that are commonly used for tablet manufacture. Unit operations include (b) (4)

Brivaracetam tablets will be supplied commercially in 35 cc (10 mg, 25 mg and 50 mg) and 60 cc (75 mg and 100 mg) HDPE bottles (60 tablet count) (b) (4) Brivaracetam tablets will also be supplied in (b) (4) Aluminum blisters for hospital unit doses and physician samples.

The drug product has an expiration dating period of 36 months when packaged in (b) (4) Aluminum blisters and HDPE bottles (b) (4) and stored at controlled room temperature conditions [25ºC (77ºF); excursions 15°C to 30ºC (59°F to 86ºF)].

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Briviact is proposed
Non Proprietary Name of the Drug Product	brivaracetam tablets
Non Proprietary Name of the Drug Substance	brivaracetam
Proposed Indication(s) including Intended Patient Population	Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older
Duration of Treatment	Chronic
Maximum Daily Dose	200 mg per day
Alternative Methods of Administration	Oral solution and intravenous infusion (pending NDAs)

D. Biopharmaceutics Considerations

1. BCS Designation: The FDA's BCS Committee granted BCS Class-1 designation to Brivaracetam Tablets 10, 25 and 50 mg in a letter dated 12/21/2007.
   - *Drug Substance:* Brivaracetam is highly soluble across the physiologic pH range of 1.2 to 7.4 (≈ 0.84 g/mL) and was demonstrated to be highly permeable during the IND stage in 2007.
   - *Drug Product:* Brivaracetam Tablets are rapidly dissolving and meet all the requirements for the BCS-Class 1 designation granted by FDA.

2. Biowaivers/Biostudies
   - *Biowaiver Requests:* The Applicant submitted a BA/BE waiver request for the following formulations/strengths on the basis of the BCS-Class 1 designation granted by FDA:

     - Capsule formulation (F1): 10, 20, 80, 150, and 200mg strengths
     - Capsule formulation (F2): 200mg strength
     - Tablet formulation (F3): 2.5 and 10mg strengths
     - Tablet formulation (F4): 25 and 100mg strengths
     - 25 and 50mg strengths (commercial formulation tablets)

     The biowaiver request for the bridging of formulations F1, F2 and F3 used in Phases 1, 2, and 3 studies with the clinical formulation, F4, is adequately supported by acceptable dissolution data; the biowaiver is therefore granted.

     (b) (4)

     the biowaiver request for the commercial 25 and 50 mg strengths tablets is also granted.

   - *PK studies:* A bioequivalence study (# EP0007) was conducted to bridge the commercial (colored, debossed) product (strengths 10, 75, 100 mg) to the clinical formulations. The results of the BE study were found acceptable and demonstrate that the proposed commercial tablets of brivaracetam have been adequately bridged to the clinical trial 50 mg strength.

   - *IVIVC:* There was no investigation of IVIVC for the proposed immediate-release drug product.

E. Novel Approaches

The applicant did not use any novel approaches or technology in the manufacture of brivaracetam drug substance or Brivaracetam Tablets.

F. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations related to product quality.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Martha R. Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
Date: 2015.08.10 19:38:22 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

Reviewer Notes on Mechanism of Action

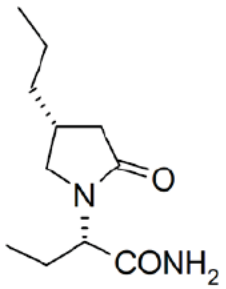
- Brivaracetam is a chemical relative (analog) of the anti-epilepsy drug levetiracetam. They both display high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A (SV2A). The binding affinity for brivaracetam is approximately 10-fold higher than for levetiracetam. Levetiracetam is the same structure as brivaracetam, but it lacks the propyl appendage in the 4-position of the lactam ring.
- Unlike levetiracetam, brivaracetam also reduces voltage-dependent sodium currents. It also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid- and glycine-induced currents.
- Brivaracetam is extensively metabolized, but seizure protection is linked to the parent compound.
- Significantly lower doses of brivaracetam are effective with respect to levetiracetam.
- Brivaracetam is the 2S,4R enantiomer. The 2S,4S enantiomer, also known as ucb 34713, which can be present in brivaracetam up to (b) (4)%, has approximately one third the binding affinity for SV2A as described in J. Med. Chem., **2004**, *47*, 530-549.

2.3.S.1 General Information

Applicant's Response:

Naming and Structure:
INN: Brivaracetam
Chemical Name: (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide
Code Names: ucb 34714 or BRV
Chemical Abstracts Registry Number: 357336-20-0

Figure 1–1: Structure of Brivaracetam



Molecular Formula: $C_{11}H_{20}N_2O_2$

Molecular Weight: 212.29
Stereochemistry: 2 chiral centers, with configuration (2S, 4R), drug substance is a single enantiomer, (b) (4)

General Properties
Appearance: white to off-white crystalline powder
Melting Point (range): 76.0 to 78.7°C
Solubility in Aqueous Media: ~0.85 g/mL in pH 1.2, 4.5 and 7.4 at 37°C (considered very soluble)
Permeability: Reported to be highly permeable. Radioactive mass balance study shows 96.8% of dose found by urinary excretion, 92.2% within 48 hours. High apparent permeability through passive diffusion was measured in vitro in Caco-2 cells. (b) (4)

LogP: 1.04
pKa: no ionizable centers
Not Hygroscopic
Specific Rotation ((b) (4)
Polymorphism:
(b) (4)

Particle Size Distribution:

- (b) (4)
  - D(v,0.5) from (b) (4) µm
  - D(v, 0.9) not more than (b) (4) µm

Reviewer's Assessment: The API is not a salt, and is water soluble and exhibits high permeability. (b) (4) [redacted] **The API is not hygroscopic. The physical properties of this API (crystalline solid with a melting point significantly higher than ambient temperature)** (b) (4) [redacted] **These are potential degradation pathways. The risk to the patient is low due to the understanding of these potential pathways, the applicant has built in appropriate controls to limit these forms of degradation. This is discussed in the manufacturing process below.**

2.3.S.2 Manufacture

(b) (4) [redacted]

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(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
Charles F. Jewell Jr. - I recommend approval from perspective of drug substance.
7/23/2015

Supervisor Comments and Concurrence:
Kasturi Srinivasachar - I concur
7/23/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Brivaracetam is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. The recommended Brivaracetam starting does is 50 mg twice daily. Based on individual patient response, the dose may be adjusted between 25 mg twice daily to 100 mg twice daily. The applicant intends to market 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg strength tablets to allow for dose adjustments. Intended to-be-marketed package configurations include both blister packs and HDPE bottles.

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

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

Brivaracetam tablets are supplied as colored, debossed 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets. The tablets are debossed on one face.

- 10 mg tablet - White to off-white round film-coated tablet debossed with "u10"
- 25 mg tablet - Grey oval film-coated tablet debossed with "u25"
- 50 mg tablet - Yellow oval film-coated tablet debossed with "u50"
- 75 mg tablet - Purple oval film-coated tablet debossed with "u75"
- 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100"

The composition of Brivaracetam tablets is provided below.

Component	Quality Standard	Function	Quantity per Tablet (b) (4)	(% w/w) (b) (4)
Brivaracetam	Oral Grade-In House	API	(b) (4)	(b) (4)
Croscarmellose sodium	NF	(b) (4)		
Lactose monohydrate	NF			
Betadex	NF			
Anhydrous lactose	NF			
Magnesium stearate	NF			
		Total	100	100

The quantity of components per tablet (b) (4) is provided below.

Quantity per Tablet (b) (4) (mg)					
Component	**10 mg**	**25 mg**	**50 mg**	**75 mg**	**100 mg**
Brivaracetam[a]	10.00	25.00	50.00	75.00	100.00
Croscarmellose Na	(b) (4)				
Lactose monohydrate					
Betadex					
Anhydrous lactose					
Magnesium stearate					
Total					(b) (4)

The qualitative and quantitative compositions of the (b) (4) film-coating agents are provided in the table below.

Components	(b) (4)				
	10 mg Tab.	**25 mg Tab.**	**50 mg Tab.**	**75 mg Tab.**	**100 mg Tab.**
Polyvinyl alcohol	(b) (4)				
Talc					
PEG 3350					
Titanium dioxide					
Iron oxide, yellow					
Iron oxide, red					
Iron oxide, black					

Reviewer's Assessment: Adequate

The drug product is available as 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg tablets. The Brivaracetam tablet (b) (4) is composed of the drug substance and various USP/NF excipients. The tablets are then coated with (b) (4) film-coating agents.

(b) (4) **Component**	**% w/w ***	**MDD (mg)**	**IIG Limit**
Croscarmellose sodium	(b) (4)		
Lactose monohydrate			
Betadex			
Anhydrous lactose			
Magnesium stearate			

*Based on 25-100 mg tablets.

There is minimal risk with each excipient as they are all below the IIG limit.

(b) (4) film coating	% w/w *	mg/tablet	IIG Limit
(b) (4)			

*Approximate quantity per tablet

Information regarding IIG limits is not available for the (b) (4) film coating. However, the primary components are in the IIG registry. Polyvinyl alcohol, talc, polyethylene glycol, and titanium dioxide make up at least (b) (4)% of the film coating. These components have an IIG limit of (b) (4) mg, respectively. There is minimal concern with the film coating as the IIG limits far exceed the maximum daily dose.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

Components of the Drug Product – Drug Substance

Brivaracetam tablets are manufactured using Brivaracetam oral grade drug substance. Brivaracetam is a white to off-white crystalline powder with a melting point of ~76°C. It is nonhygroscopic, (b) (4) (b) (4)

Brivaracetam is highly permeable and soluble. It is classified as 'Class 1' according to the BCS.

The particle size of Brivaracetam is controlled in the drug substance specification to ensure uniformity in the finished product.

(b) (4)

Long term and accelerated stability studies of Brivaracetam (oral grade) under ICH conditions have been performed following 36 months storage. The data demonstrate excellent stability to heat, light, and humidity exposure.

Components of the Drug Product - Excipients

The excipients used to manufacture Brivaracetam tablets are lactose monohydrate, anhydrous lactose, betadex (β-cyclodextrin), croscarmellose sodium, magnesium stearate, (b) (4) and different commercially available film-coating agents (b) (4) All the excipients are

commonly used and are compendial substances or commercially available film-coating agents comprising of compendial substances.

Excellent excipient-drug substance compatibility was demonstrated via binary mixtures of Brivaracetam with excipients and overall compatibility during stability studies on Brivaracetam tablets.

These excipients have been selected based on scientific knowledge (b) (4) , formulation development studies, and the experience with other products developed by UCB. Excipient concentrations are within the recommended ranges.

Drug Product

(b) (4)

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OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The drug product data is adequate to support approval from a quality perspective.

Andrei Ponta
28-Jul-2015

Supervisor Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.; Branch Chief (Acting), Branch I, DNDP, ONDP
July 31, 2015

ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Batch Formula

The following table shows the batch formula:

(b) (4)

[redacted]

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The application does not include any Comparability Protocols

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature: Bogdan Kurtyka, 07/09/2015
Drug product manufacturing process is well understood and controlled. The manufacturing process development successfully identified process parameters and in-process controls to assure acceptable drug product quality. These parameters were successfully scaled up and implemented for the commercial process.

Supervisor Comments and Concurrence: Sharmista Chatterjee, 07/10/2015
I concur.

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

31. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.
- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how the potential issues identified above, were/were not mitigated.

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)				*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk	GMP Inspection (b) (4), 2 item 483, firms corrective and preventive actions were adequate	Acceptable

				process		
			(b) (4)	*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	Surveillance Inspection Conducted (b) (4) No FDA 483	Acceptable
UCB Pharma Belgium	3003909356	CSN	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability	(b) (4) *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	Inspection Scheduled September 2015	Pre-Approval(PAI) inspection is required

			testing of drug substance			

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
			(b) (4)	8	6	30	44
				8	6	30	44
UCB Pharma Belgium	3003909356	CSN	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	2	6	30	38

(b) (4)

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(b) (4) There were no issues that appeared significant or that would cause quality issues to this product. The product sub-score and overall risk evaluation above shows up in red because the product is an NME which is a flag to determine if there are additional concerns that would warrant the need for an inspection. The process at this site is considered to be low risk since the only responsibility is to perform release testing and stability testing. A routine inspection is required in order for the GMP status to be current since the last inspection was in (b) (4) A GMP surveillance inspection is scheduled to take place the last week of (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant outstanding manufacturing risks that will affect this application. Pre-approval inspection coverage is required for **UCB Pharma (FEI 3003909356)** in addition to GMP coverage for (b) (4) however, there are no anticipated concerns that will possibly affect the approval of this application going into the inspection. The UCB and (b) (4) inspections are scheduled for completion by the "GRMP" date for NME NDA facility inspections and the overall facility recommendations will be made at that time.

Ebern Dobbin
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Supervisor Comments and Concurrence:

Concur with initial assessment, final assessment following completion of inspection activities for UCB and (b) (4)

Mahesh Ramanadham, 8/10/15.

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

Drug Substance

Brivaracetam has two chiral centers and it is said to be the diastereoisomer of the four stereoisomers. (b) (4)

Brivaracetam is very soluble across the physiologic pH range (see table below); it is also highly permeable and has been designated by the Agency's BCS Committee as a BCS Class 1 drug substance. For additional details on brivaracetam, please refer to the CMC drug substance review.

	pH 1.2	pH 4.5	pH 7.4
Volume (mL of media) required to dissolve 200 mg of brivaracetam	0.03	0.03	0.03
Brivaracetam solubility (g/mL of solution)	0.84	0.85	0.84

Drug Product

The proposed drug product for commercialization is a film-coated tablet containing 10, 25, 50, 75 or 100 mg of brivaracetam. The strengths are visually distinguishable by their colors. It should be noted that four formulations (F1, F2, F3, & F4) were made during development; F2-F4 were used in Phases 1 – 3 studies. The quantitative composition of the final drug product is presented in the table below; (b) (4) Please refer to the CMC drug product review for additional details.

Component	Quality Standard	Function	Quantity per Tablet (mg)				
Tablet (b) (4)			10 mg	25 mg	50 mg	75 mg	100 mg
Brivaracetam	Oral grade In-house	Active ingredient	10.00*	25.00*	50.00*	75.00*	100.00*
Croscarmellose sodium	NF	(b) (4)					
Lactose monohydrate	NF						
Betadex	NF						
Anhydrous lactose	NF						
Magnesium stearate	NF						
Film Coating			Approximate Quantity per Tablet (mg)				
			(b) (4)				

(b) (4)

Two additional dosage forms were developed and submitted to FDA. Currently, these additional dosage forms [10 mg/mL Oral Solution (NDA 205838) and 10 mg/mL Solution for Intravenous Administration (NDA 205837)] are undergoing review in parallel with this NDA.

33. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

The Applicant developed a dissolution method for use to support the bridging between the different formulations used during the phases of development. However, a proposal to replace the dissolution test with a disintegration test is included in the application. The adequacy of this proposal is being assessed in this review and no further rigorous review of the dissolution method was deemed necessary. Nevertheless, it is pertinent to mention that the dissolution data at release and in the stability program demonstrated rapid dissolution for all the proposed strengths of Brivaracetam Tablets over 24 months; the data are in agreement with the BCS Class 1 designation for the drug product.

Dissolution Method

The Applicant's initial proposed dissolution testing conditions can be summarized as follows:

Apparatus:	(b) (4)
Medium:	
Temperature:	
Rotation speed:	
Sampling Times	
Proposed Spec Sampling Times:	
Analysis:	
Proposed specs:	

As stated earlier, (b) (4) the Applicant is proposing not to use dissolution as a release test. However, the following media were used for comparative dissolution testing of the various formulations during drug product development (individual vessel data are provided in Module 3, section 3.2.P.2.2): (b) (4) In all testing conditions, more than (b) (4)% brivaracetam was release in less than (b) (4) min except for the 100 mg F4 formulation (in pH (b) (4) and the 50 mg at pH (b) (4) The (b) (4) was used as the medium for disintegration testing.

Disintegration Method and Applicant's Proposed Acceptance Criterion

The Applicant is proposing to adopt the USP<701> disintegration test and proposes a disintegration acceptance criterion of "NMT (b) (4) min" in the Specifications table of the Drug Product. The Applicant referenced the conditions stipulated in ICH Q6A Guidance to justify adopting a disintegration test as a surrogate for dissolution. In particular, the Applicant asserted that a correlation between dissolution (at (b) (4) min) and disintegration was established (see Figure 1). In general, the Applicant's rationale for proposing disintegration testing (over dissolution) is that all individual vessel % brivaracetam dissolved values were greater than (b) (4) % in less than (b) (4) min throughout the 24-month stability program under all storage conditions and packaging configurations.

Figure 32-1: Correlation of dissolution and disintegration for registration batches of Brivaracetam Tablets over 24 months (from Fig 1-2, section 3.2.P.5.6 of the NDA).

Reviewer's Comments:
The Applicant's proposal to replace dissolution with disintegration seems reasonable due to the rapid dissolution of Brivaracetam Tablets. However, the correlation depicted in Figure 1 could not be verified. In addition, the discriminating power of the disintegration test was not provided. The following IR comments were therefore sent to the Applicant on 03/18/2015:

i. Although the proposal to replace dissolution with disintegration as a release test and in the stability protocol seems reasonable due to the rapid dissolution of Brivaracetam Tablets, the correlation between disintegration and dissolution could not be verified. In addition, there are no data in the NDA to support a greater discriminating power of disintegration over dissolution. Provide the raw (individual vessel) data used to establish the correlation between dissolution and disintegration that is depicted in Figure 1-2 in section 3.2.P.5.6, and provide a comprehensive description of the quantitative relationship between the two test methods. Alternatively, provide data to demonstrate that disintegration is a more discriminating test than dissolution.

ii. Provide the individual vessel disintegration data for the clinical and primary (as well as secondary) stability batches at release and during stability that support the proposed disintegration acceptance criterion of "NMT (b) (4) min". Present the data graphically and in tabular format accompanied by a scientific rationale that supports the proposed acceptance criterion.

iii. Justify the use of (b) (4) as the medium for disintegration testing. Note that disintegration of Brivaracetam occurs (b) (4) the disintegration medium is not acceptable.

Applicant's Responses to the IR Comments of 03/18/2015:
The Applicant responded to the IR comments on 4/24/2015 and updated the responses in a supplementary amendment to the NDA on 5/29/2015.

Applicant's Response to IR Comment (i):

The Applicant cited the ICH Q6A guidance as the basis for the proposal to replace dissolution with disintegration for routine batch release testing. Accordingly, the following criteria were stated as the scientific basis for the proposal:

- Brivaracetam tablets are immediate-release;
- The drug substance is highly soluble across the physiologic pH range of 1.2 – 6.8 (b) (4));
- In dissolution testing, more than (b) (4) % brivaracetam is dissolved within (b) (4) min at pH (b) (4) under all storage conditions and at all stability time points;
- Dissolution has no impact on brivaracetam bioavailability;
- A 'link' or correlation exists between disintegration and dissolution; and
- Although both dissolution and disintegration are insensitive to changes in process parameters (b) (4) , the latter is likely to be more discriminating than the former.

The Applicant submitted all of the requested data sets.

Reviewer's Evaluation:

The Applicant met most of the requirements stipulated in the ICH Q6A guidance for use of disintegration as a surrogate for the dissolution test. However, the Applicant's claim of a correlation between the two tests as depicted in Figure 1 is neither supported by the data submitted nor substantiated in the two IR responses. That notwithstanding, this Reviewer agrees that a disintegration test is likely to be more clinically meaningful for Brivaracetam Tablets provided the test is adequately controlled with an appropriate limit.

Applicant's Response to IR Comment (ii):

According to the Applicant, disintegration data were not initially generated on the clinical and secondary stability batches since it was not a proposed test at the time. Disintegration data over 30 months were submitted for the Primary stability batches; data for 11 validation batches were also submitted. Following collation of the data, the Applicant tightened the disintegration time acceptance criterion from NMT (b) (4) min to NMT (b) (4) min. The individual vessel disintegration data are presented graphically in Figures 32-2 and 32-3.

Figure 32-2: Individual vessel disintegration data (over 30 months) for Primary stability batches of Brivaracetam Tablets, 25 mg

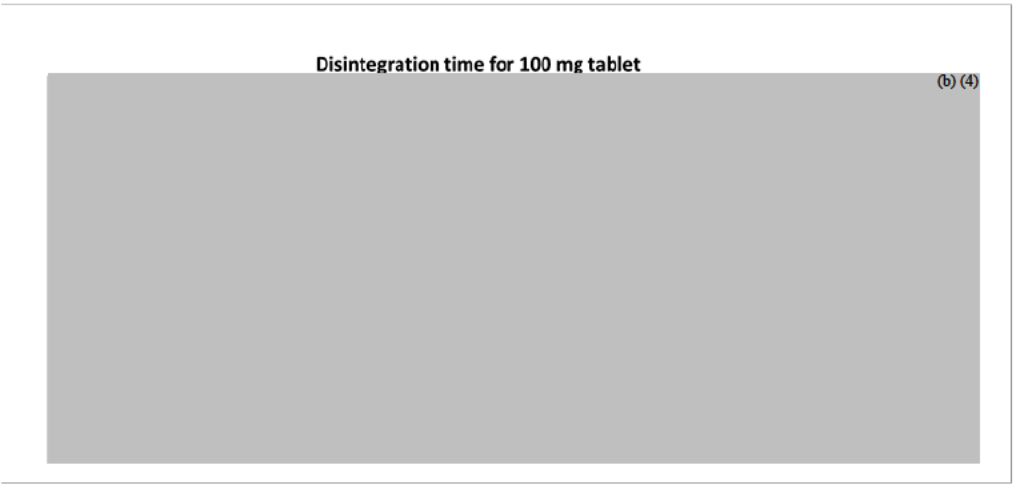


Figure 32-3: Individual vessel disintegration data (over 30 months) for Primary stability batches of Brivaracetam Tablets, 100 mg.

The maximum disintegration time observed in the 100 mg validation batches was (b) (4) min.

Reviewer's Evaluation:
Based on the data submitted (displayed in Figures 2, 3, and 4 above), this Reviewer recommends a disintegration time acceptance criterion of NMT (b) (4) min for all strengths of Brivaracetam Tablets.

Recommended Disintegration Time Acceptance Criterion for Brivaracetam Tablets,10, 25, 50, 75, 100 mg.
NMT (b) (4) min

Applicant's Response to IR Comment (iii):

[redacted] In the April 24, 2015 response, the Applicant stated that disintegration testing in pH [redacted] was planned and that results were to be submitted to the NDA by May 29, 2015. The response submitted on 5/29/2015 did not contain the data. Therefore, the following IR comments were sent to the Applicant on July 7, 2015 to address this issue:

i. FDA agrees that the use of the same medium for dissolution and disintegration testing during drug product development is meaningful. However, if disintegration is found acceptable for routine QC/Stability testing, [redacted] The response to the IR comments submitted on 5/29/2015 did not contain results of the planned multimedia disintegration study, in 0.1 N HCl (pH 1.2), [redacted] submit these data [redacted] for disintegration testing. If the comparative disintegration time data have already been submitted, please refer to their location in your response.

ii. Note that if disintegration testing, in lieu of dissolution, is found adequate, the proposed disintegration time acceptance criterion of "NMT [redacted] min" will not be accepted by FDA. Based on the data submitted in the 4/24/2015 response, FDA recommends that the proposed acceptance criterion should be further tightened to "NMT [redacted] min"; inadequate control of the disintegration time eliminates the potential for better discrim ating power relative to dissolution.

Applicant's Responses to the IR Comments of 07/7/2015:
The Applicant responded to the IR comments on 7/13/2015; the disintegration medium has been changed to 0.1N HCl and the proposed acceptance criterion revised to NMT [redacted] min. Both changes have been made to the Specifications Table.

Reviewer's Evaluation:
Although the use of the same medium for dissolution and disintegration testing during drug product development is meaningful, since dissolution is no longer needed in routine QC/Stability testing, [redacted] *The Applicant had changed the disintegration medium to 0.1N HCl and the acceptance criterion has been tightened to NMT [redacted] min. Both changes are reflected in the updated Specifications Table and are acceptable.*

34. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

The proposed commercial formulation (colored, debossed tablets) is different from the various formulations used in Phases 1, 2, and 3 clinical studies. Therefore, bioequivalence study EP0007 was conducted to support the bridging of the commercial product (strengths 10, 75, 100 mg) to the clinical formulations. The list of formulations and summaries of their differences are displayed below in Table 33-1.

Table 33-1: Solid oral dosage forms of brivaracetam manufactured during development.

Formulation	Dosage Form	Dosage Strengths (mg)	Qualitative Composition	Clinical Use
F1	Capsule	10, 20, 40, 80, 100, 150, 200	(b) (4)	Formulation used in Phase 1 & 2a clinical
F2	Capsule	25, 50, 200		Formulation used in Phase 1 & 2b clinical studies
F3	Round Film coated Tablet (b) (4)	2 5 10		Formulations used in Phase 1, 2b & 3 clinical studies
F4	Oval Film coated Tablet (b) (4)	10 25 50 100		Formulations used for Phase 1, 2 & 3 clinical studies (The 100 mg tablet was not used in any clinical studies)
Colored debossed tablets Intended for commercialization	Round film coated tablet (10 mg) Oval film coated tablet (other strengths) (b) (4)	10 25 50 75 100	**Tablet** (b) (4) Brivaracetam, sodium croscarmellose, betadex, lactose monohydrate, lactose anhydrous, magnesium stearate **Film coating:** (b) (4)	Colored debossed tablets 10 mg, 75 mg and 100 mg were used in Phase 1 clinical studies

All the formulations (F1, F2, F3, F4, and Commercial tablets) exhibited rapid dissolution (> (b) (4) %) at pH (b) (4) indicative of the rapidly dissolving characteristic of the drug product. Since the drug product was designated as BCS-1, comparative dissolution testing would normally be sufficient to bridge the commercial and clinical formulations; however, the 75 and 100 mg strengths were yet to be manufactured at the time the BCS-1 designation was granted by FDA's BCS Committee.

The in-vivo bridging BE study for the commercial colored, debossed tablets is summarized below.

Study No. E0007 : Bridging Bioequivalence Study of the clinical formulation and the proposed commercial tablets.

Study Title: A randomized, single-center, open-label, 5-way crossover, single-dose bioavailability/bioequivalence comparison of brivaracetam oral tablets (10mg, 50mg, 75mg, and 100mg) and brivaracetam intravenous bolus injection (100mg) in healthy volunteers.

Design: Phase 1, single-dose, randomized, single-center, open-label, 5-way, crossover.
n = 25 healthy subjects
Treatments: 5 Treatment Periods, separated by Wash-Out of at least 7 days:

- 1x100mg solution for injection (as 2-minute iv bolus injection)
- 1x100mg tablet (commercial formulation)
- 1x75mg tablet (commercial formulation)
- 1x50mg tablet (clinical development formulation F4)
- 1x10mg tablet (commercial formulation)

Blood samples were collected to determine the brivaracetam plasma concentrations up to 48h after dosing.

Results:
Brivaracetam mean plasma concentration-time curves (n = 25) for all treatments are presented in Figure 33-1 below.

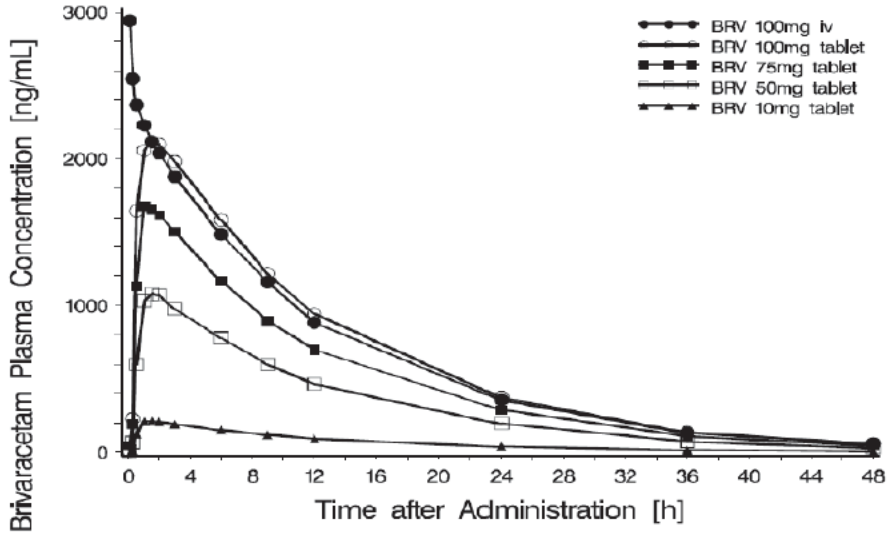


Figure 33-1: Geometric mean brivaracetam plasma concentration-time profiles for brivaracetam tablets and solution for injection in healthy volunteers (Study # EP0007).

The mean brivaracetam PK parameters are shown in Table 33-2 and results of the statistical analyses are presented in Table 33-3.

Table 33-2: Mean brivaracetam PK parameters for brivaracetam tablets and solution for injection in healthy volunteers (Study # EP0007; n = 25).

	BRV				
	10mg tablet n=25	50mg tablet n=25	75mg tablet n=25	100mg tablet n=24	100mg iv n=25
Parameter (unit)	Geometric mean (geometric CV [%])				
AUC (h.ng/mL)	3123 (25.6)	15712 (25.7)	23791 (24.9)	31491 (25.0)	31042 (24.8)
AUC_{norm} (h.ng/mL)	15615 (25.6)	15712 (25.7)	15861 (24.9)	15746 (25.0)	15521 (24.8)
$AUC_{(0-t)}$ (h.ng/mL)	3015 (24.4)	15227 (24.9)	23099 (24.0)	30652 (24.1)	30193 (23.9)
$AUC_{(0-t)norm}$ (h.ng/mL)	15073 (24.4)	15227 (24.9)	15399 (24.0)	15326 (24.1)	15097 (23.9)
C_{max} (ng/mL)	240 (21.4)	1236 (27.8)	1941 (23.9)	2570 (22.4)	3170 (35.3)
$C_{max,norm}$ (ng/mL)	1198 (21.4)	1236 (27.8)	1294 (23.9)	1285 (22.4)	1585 (35.3)
CL/F (L/h)	3.20 (25.6)	3.18 (25.7)	3.15 (24.9)	3.18 (25.0)	3.22 (24.8)
Vz/F (L)	44.5 (18.7)	42.9 (21.8)	41.9 (20.6)	40.9 (20.0)	42.3 (20.1)
$t_{½}$ (h)	9.64 (14.8)	9.34 (12.8)	9.20 (13.0)	8.92 (13.8)	9.11 (13.9)
	Median (range)				
%AUC (%)	2.9 (1.2, 7.1)	2.7 (1.4, 7.3)	2.5 (1.3, 6.9)	2.3 (0.9, 5.5)	2.2 (1.1, 7.5)
t_{max} (h)	1.00 (0.50, 2.00)	1.00 (0.25, 2.00)	1.00 (0.25, 3.00)	1.00 (0.50, 3.00)	0.08 (0.08, 1.50)

Table 33-3: Bioequivalence comparisons of brivaracetam commercial tablets (10, 75, 100mg) and solution for injection vs 50 mg clinical tablet batch (F4); n = 25

Parameter (unit)	Test BRV	Reference BRV	Residual CV (%)[a]	Test/Reference[b]	
				Point estimate	90% CI[b]
$C_{max,norm}$ (µg/mL)	10mg comm. tablet	50mg tablet F4	16.7	0.969	0.897, 1.048
	75mg comm. tablet	50mg tablet F4		1.047	0.969, 1.132
	100mg comm. tablet	50mg tablet F4		1.056	0.976, 1.143
	100mg solution for injection	100mg comm. tablet		1.214	1.122, 1.314
		50mg tablet F4		1.283	1.187, 1.386
$AUC(0-t)_{norm}$ (µg.h/mL)	10mg comm. tablet	50mg tablet F4	4.4	0.990	0.970, 1.011
	75mg comm. tablet	50mg tablet F4		1.011	0.991, 1.033
	100mg comm. tablet	50mg tablet F4		1.022	1.001, 1.044
	100mg solution for injection	100mg comm. tablet		0.970	0.950, 0.991
		50mg tablet F4		0.991	0.971, 1.012
AUC_{norm} (µg.h/mL)	10mg comm. tablet	50mg tablet F4	4.6	0.994	0.973, 1.015
	75mg comm. tablet	50mg tablet F4		1.009	0.988, 1.031
	100mg comm. tablet	50mg tablet F4		1.017	0.995, 1.039
	100mg solution for injection	100mg comm. tablet		0.971	0.950, 0.993
		50mg tablet F4		0.988	0.967, 1.009

The PK parameters were normalized to the 50 mg dose prior to ANOVA and computation of 90% geometric confidence intervals.

Applicant's Conclusions:

- The 3 new commercial BRV tablets (BRV 10mg, 75mg, and 100mg) were bioequivalent with respect to the BRV 50mg clinical development tablet used as a reference.
- The BRV 100mg iv bolus injection had similar bioavailability to the BRV 50mg and 100mg tablets.
- Brivaracetam 100mg iv was bioequivalent to BRV 50mg and 100mg tablets with regards to AUCnorm (BRV 50mg 90% CI: 0.9969 to 1.0092; BRV 100mg 90% CI: 0.9504 to 0.9925), but not Cmax, which was approximately 20% higher than oral formulations (BRV 50mg 90% CI: 1.1867 to 1.3863; BRV 100mg 90% CI: 1.1222 to 1.3136).
- Single doses of BRV were generally well tolerated with no TEAEs reported as severe, serious, or leading to subject discontinuation; no deaths occurred.

Reviewer's Assessment:
The results of the bioavailability/bioequivalence study are acceptable and demonstrate that the proposed commercial tablets of brivaracetam have been adequately bridged to the clinical trial 50 mg strength.

33-1. Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

The Applicant submitted a BA/BE waiver request for the following formulations/strengths on the basis of the BCS-1 designation granted by FDA:

- Capsule formulation (F1): 10, 20, 80, 150, and 200mg strengths
- Capsule formulation (F2): 200mg strength
- Tablet formulation (F3): 2.5 and 10mg strengths
- Tablet formulation (F4): 25 and 100mg strengths
- 25 and 50mg strengths (commercial formulation tablets)

All the formulations (F1, F2, F3, F4, and Commercial tablets) exhibited rapid dissolution (> (b) (4) %) at pH (b) (4) indicative of the rapidly dissolving characteristic of a BCS-Class 1 designated drug product.

Reviewer's Assessment:
The BE study waiver request for the bridging of formulations F1, F2, F3 used in the Phase 1, 2, and 3 studies with the clinical formulation F4 is supported with acceptable dissolution data and therefore the biowaiver is granted.

(b) (4)

the BA waiver request for the commercial 25 and 50 mg strengths tablets is also granted.

Biopharmaceutics Reviewer's Overall Assessment:

Brivaracetam is a diastereoisomer. (b) (4) The proposed drug product is also highly permeable and has been designated by the FDA's BCS Committee as a BCS Class 1 drug substance/drug product. The biopharmaceutics review is summarized as follows:

- ***Adequacy of disintegration testing in lieu of dissolution testing:***

The Applicant proposed to use disintegration testing in lieu of dissolution testing, because for all the individual vessels the percent of brivaracetam dissolved values were greater than (b) (4)% in less than (b) (4)min throughout the 24-month stability program for all strengths under all storage conditions and packaging configurations. Most of the requirements stipulated in the ICH Q6A guidance for use of disintegration as a surrogate for the dissolution test were met. However, the Applicant's claim of a correlation between the two tests is neither supported by the data nor substantiated in the two IR responses. That notwithstanding, this Reviewer agrees that a disintegration test is likely to be more clinically meaningful for Brivaracetam Tablets provided the test is adequately controlled with an appropriate limit. The Applicant initially proposed the use of (b) (4) as the medium; upon receiving the July 7, 2015 IR ((b) (4), the Applicant updated the Specifications table to reflect a proposal to use 0.1N HCl as the disintegration medium. This is acceptable.

- ***Disintegration time acceptance criterion:***

Based on the Applicant's July 13, 2015 response to the final biopharmaceutics IR, the agreed upon final disintegration time acceptance criterion is NMT (b) (4)min.

- ***Bridging of TBM product to earlier formulations:***

The to-be-marketed formulation has been adequately bridged to the clinical formulation through in-vitro dissolution testing, a BE waiver, and an in-vivo bioequivalence study.

- ***Evaluation of BA waiver request:***

The Applicant's biowaiver request for the commercial 25 and 50 mg strengths has been granted (b) (4)

- ***Risk Assessment Evaluation:***

Brivaracetam is highly soluble and highly permeable and the drug product dissolves in dissolution media (b) (4) within (b) (4) min. In addition, the disintegration time of the tablets is also rapid (less than (b) (4)min). From a biopharmaceutics perspective, Brivaracetam IR tablets are therefore considered to be a low risk drug product. Please refer to the CMC review for the overall quality risk assessment table for this drug product.

Initial Risk Assessment			Final Risk Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Dissolution/ Disintegration	None	Low	N/A	Acceptable	None. The drug product is rapidly dissolving and correlates qualitatively to a rapid in-vivo absorption.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The disintegration test, as described in USP<701> and using 0.1N HCl as the medium, is approved for use in batch release testing of all strengths of Brivaracetam Tablets with an acceptance criterion of "NMT (b) (4) min". The Division of Biopharmaceutics recommends APPROVAL of NDA 205836 for Brivaracetam Tablets 10, 25, 50, 75, and 100 mg.

Okpo Eradiri, Ph. D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:

I concur with Dr. Okpo Eradiri's Biopharmaceutics overall assessment and recommendation.

Angelica Dorantes, Ph. D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: This is a non-sterile oral tablet. The release specifications and the stability program do not include testing for microbial quality and the exclusion of these tests was justified based on the decision tree #8 of ICH Guidance Q6A. The historical bioburden data was provided for the clinical lots produced to date. More information on their process will be needed.

The 74-day letter included the following information request:

1. We note that microbial limits testing is not included in either the drug product specification or the post approval stability protocol. If you propose to waive microbial limits release and stability testing for your drug product, this proposal may be acceptable provided adequate upstream controls are established and documented. More information on your process is needed. Address the following points.

    a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

    (b) (4)

    b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

    c. Describe activities taken when microbiological acceptance criteria are not met at control points.

2. If you elect to perform microbial limits testing for drug product release and stability, please submit revised a drug product specification and stability protocol indicating microbial limits testing and corresponding acceptance criteria, as well as methods suitability verification data for the microbiological methods used to demonstrate the microbiological quality of the drug product.

Summary of Response: Information was provided regarding (b) (4) Additionally (b) (4) was provided. (b) (4)

Reviewer's Note: (b) (4) Bioburden results for the (b) (4) clinical lots all met the USP specifications for a non-aqueous oral dosage form for Total Aerobic Microbial Count, Total Yeast and Mold Counts and for the Absence of Escherichia coli. The sponsor updated the release specifications and stability protocol to perform microbial limit testing (b) (4) . This results (b) (4) which is not acceptable. An information request was sent requesting that the bioburden testing (b) (4) be (b) (4) a stability specification.

Information request of 22 May 2015 Question 1: We have received your response in NDA 205836 dated March 10, 2015, in which you proposed to test bioburden (b) (4) which is not acceptable per 21 CFR 211.165 (a) and (b). Amend the application to have the bioburden test as a stability test (b) (4)) in the stability protocol (section P.8) (b) (4) Provide the method suitability report supporting the bioburden testing.

Summary of Response: UCB amended the application (b) (4) and retained the bioburden as a stability test. The method suitability supporting the bioburden testing was amended to section 3.2.P.5.3 of the application.

Review of response: The sponsor has amended the release specification as requested. The bioburden testing (b) (4) remains in the stability program. The method suitability was amended into section 3.2.P.5.3. The method suitability was performed per USP <61> and <62> on three batches of brivaracetam tablets using the USP indicator organisms. The method suitability met the acceptance criteria and supports the routine bioburden testing of brivaracetam tablets.

-ADEQUATE-

Reviewer Note: The sponsor has provided adequate information supportive of the low risk of the product for microbial contamination in the manufacturing process and in the historical testing results. The continuation of microbial testing of the product in the stability program is acceptable. The bioburden testing method is supported by the method suitability testing.

2.3.P.6 Reference Standards or Materials

36. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: NA, container closure is not a critical attribute for this dosage form from a quality microbiology perspective.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

37. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: NA

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: There were no quality microbiology deficiencies identified in the information provided. The application is recommended for approval from a quality microbiology perspective.

Denise A. Miller, Microbiology Reviewer 06/24/15

Supervisor Comments and Concurrence:

Neal J. Sweeney, Ph.D. 7/27/15
Acting Microbiology Quality Assessment Lead
OPQ/OPF/DMA/Branch 2

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Evaluation by Drug Product Reviewer:

1. Is the applicant's claim for categorical exclusion acceptable?
2. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

This NDA is subject to categorical exclusion under 21 CFR 25.31(b). Therefore, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

UCB certifies that, to the best of our knowledge, no extraordinary circumstances exist where the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(d).

The proposed action complies with the following categorical exclusion criterion: the Expected Introduction Concentration (EIC) for Brivaracetam in the aquatic environment is below 1 ppb.

The mathematical formula used for calculation of the EIC was that recommended in the "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" (Center for Drug Evaluation and Research, July, 1998, page 4). The calculation of the EIC is based on the highest quantity of the active moiety expected to be produced for use in any of the next five years.

Calculation of the EIC of Brivaracetam in the Aquatic Environment:

EIC–Aquatic (ppb) = A x B x C x D

Where A = kg/year production (as active moiety); B = 1/liters per day entering POTWs*; C = year/365 days; D = 109 µg/kg (conversion factor)

*1.214 x 1011 liters per day entering publicly owned treatment works (POTW's); Source: 1996 Needs Survey, Report to Congress.

The value of the parameters A, B, C and D are as follows:

A = (b) (4) kg (5th year production); B = (b) (4); C = (b) (4); D = 109 µg/kg (conversion factor)

EIC – Aquatic (ppb) = A x B x C x D = (b) (4) ppb ((b) (4) ppb)

Conclusion - the EIC of Brivaracetam in the aquatic environment is < 1 ppb. Based on the EIC, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

I. Review of Common Technical Document-Quality (CTD-Q) Module 1

Evaluation by Drug Product Reviewer:

Labeling & Package Insert

I. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Item	Information Provided in NDA		Reviewer's Assessment
Product title, Drug name (201.57(a)(2))			
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		The proposed proprietary name is Briviact.
Dosage form, route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Controlled drug substance symbol (if applicable)	NA		NA
Dosage Forms and Strengths (201.57(a)(8))			
A concise summary of dosage forms and strengths	Brivaracetam drug products are available as film coated tablets, an oral solution, and a solution for injection. Immediate release tablets containing 10 mg, 25 mg, 50 mg, 75 mg and 100 mg of Brivaracetam have been developed. The oral solution contains 10 mg/mL of Brivaracetam. Brivaracetam solution for injection is provided in a single-use vail containing 50 mg of Brivaracetam in 5 mL of solution (10 mg/mL).		**The label and information provided in NDA are in agreement. However, the sponsor does not provide subheadings (e.g., injectable, capsule).**

NA = Not Applicable

Conclusion:

The label is accurate and consistent with the information provided in the NDA. However, the label does not include subheadings per CFR 201.57(a)(8).

Information to be Requested

- Adequate subheadings are not included in the package insert highlights section, under the dosage forms and strengths portion. CFR 201.57(a)(8) requires a concise summary with "any appropriate subheadings (e.g., tablets, capsules, injectable, suspension)." Differentiate between the oral solution and the solution for injection. Specifically, indicate that the single-use vial is to be used for injection.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA			Reviewer's Assessment
Available dosage forms	Tablets	Oral Solution	Solution for Injection	The label and information provided in NDA are in agreement.
Strengths: in metric system	10 mg; 25 mg; 50 mg; 75 mg; and 100 mg	10 mg/mL	50 mg/ 5 mL	The label and information provided in NDA are in agreement.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face • 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution			The label and information provided in NDA are in agreement.

Conclusion:

The label is accurate and consistent with the information provided in the NDA.

#11: Description (21CFR 201.57(c)(12))

(b) (4)

Item	Information Provided in NDA		Reviewer's Assessment
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		Briviact is the proposed proprietary name.
Dosage form and route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA		NA
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tablets Tablets contain sodium croscarmellose, lactose monohydrate, betadex (β-cyclodextrin), anhydrous lactose, and magnesium stearate. Tablets are coated with the following materials: 10 mg tablets - polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide 25 mg and 100 mg tablets - polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, black iron oxide 50 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide 75 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide, black iron oxide Oral Solution It contains: sodium citrate, anhydrous citric acid, methylparaben, sodium carboxymethylcellulose, sucralose, sorbitol solution, glycerin, raspberry flavor, and purified water. Solution for Injection It contains: sodium acetate (trihydrate), glacial acetic acid (for pH adjustment to 5.5), sodium chloride and water for injection		The label and information provided in NDA are in agreement.
Statement of being sterile (if applicable)	Brivaracetam solution for injection is supplied as a clear, colorless liquid supplied as a sterile, preservative-free solution.		The label and information provided in NDA are in agreement.
Pharmacological/ therapeutic class	Antiepileptic		**The label is missing this information.**
Chemical name, structural formula, molecular weight	The chemical name is (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide. Its molecular formula is $C_{11}H_{20}N_2O_2$ and its molecular weight is 212.29.		The label and information provided in NDA are in agreement.
Radioactivity	NA		NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Brivaracetam, a white to off-white crystalline powder, is very soluble in aqueous media across the range pH 1.2 to pH 7.4 (b) (4) It is also very soluble in ethanol and freely soluble in acetonitrile. It is very slightly soluble		The label and information provided in NDA are in agreement.

	in n-hexane (b) (4) . Brivaracetam is a chiral molecule. (b) (4) .	

Conclusion:

The label contains the placeholder "TRADENAME" for the proprietary name. The sponsor has proposed Briviact as the proprietary name for Brivaracetam.

(b) (4)
. However, this is not required under 21CFR 201.57(c)(12).

The therapeutic class information is missing under the description heading. The sponsor will be asked to update the label accordingly. The remaining label information is accurate and consistent with the information provided in the NDA.

Information to be Requested

- Information regarding the pharmaceutical/therapeutic class is absent in the package insert description section (#11). According to CFR 201.57(c)(12), the description section must contain the pharmacological or therapeutic class of the drug. Please update the label with the appropriate information.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 **HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied

(b) (4)

16.2 Storage

Store at 25 °C (77 °F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not freeze TRADENAME injection or oral solution.

Discard any unused TRADENAME oral solution remaining after 5 months of first opening the bottle.

Item	Information Provided in NDA		Reviewer's Assessment
Strength of dosage form	Strength:	Dosage Form:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Available units (e.g., bottles of 100 tablets)	Tablets: 35 cc (10 mg, 25 mg and 50 mg) and 60 cc (75 mg and 100 mg) bottles (60 tablet count) Oral Solution: 300 mL bottle Solution for Injection (b) (4) mL single-use vial		The label and information provided in NDA are in agreement.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face		There is currently a placeholder for the NDC-number. The label and information provided in NDA are in agreement.

	• 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution	
Special handling (e.g., protect from light, do not freeze)	The drug product is stable to short term excursions between [redacted] (b) (4).	The label includes the additional instructions "do not freeze" for the oral solution and solution for injection drug product.
Storage conditions	Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	The label and information provided in NDA are in agreement.

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

TRADENAME Tablets, TRADENAME Oral Solution, and TRADENAME Injection manufactured for
UCB, Inc.
Smyrna, GA 30080

TRADENAME is a registered trademark of the UCB Group of Companies
© 20XX, UCB, Inc., Smyrna, GA 30080
All rights reserved.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	UCB Pharma S.A.	The label and information provided in NDA are in agreement.

Conclusion:

The label includes the special handling instructions, "do not freeze" for the oral solution and solution for injection. This is acceptable.

The label is accurate and consistent with the information provided in the NDA.

II. Labels

1) Immediate Container Label

Blister Pack Labeling – Professional Sample

1 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The number of tablets is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The label bears the "Rx only" statement.	Adequate
Storage (not required)	The label has the following storage conditions instructions: Controlled room temperature conditions [25ºC (77ºF); excursions 15 – 30ºC (59 – 86ºF)]	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the label.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
Others	NA	NA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The label is accurate and consistent with the information provided in the NDA. All CFR requirements are met.

2) Cartons

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The number of tablets is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	NA	NA
Sterility Information (if applicable)	NA	NA
"Rx only" statement per 21 CFR 201.100(b)(1)	The carton bears the "Rx only" statement.	Adequate
Storage Conditions	The label has the following storage conditions instructions: Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	(b) (4)	**Inadequate**
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	A "See accompanying prescribing information" statement is included on the side of the package.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	The blister cartons contain a "Keep out of reach of children" statement. This statement is not included on the cartons for the bottles.	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	The drug product is for oral use.	Adequate

Conclusion:

The label is accurate and consistent with the information provided in the NDA. All CFR requirements are met.

II. List of Deficiencies To Be Communicated

There are no deficiencies to be communicated at this time.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

(b) (4)

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	L	Not applicable	Acceptable	
Physical stability (solid state)	Formulation, process parameters, moisture	M	(b) (4)	Acceptable	
Content uniformity	Low dose, particle size/shape, segregation, flow property	L	Not applicable	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	L	Not applicable	Acceptable	
Dissolution/ Disintegration	Particle size, moisture, hardness, size, shape, film coat	L	Not applicable	Acceptable	None. (b) (4)

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

NDA 205837
Review # 1

Drug Name/Dosage Form	Brivaracetam Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	UCB Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Quality Amendment	12/22/14
Quality Amendment	1/12/15
Quality Amendment	3/10/15
Quality Amendment	5/20/15
Quality Amendment	6/10/15
Quality Amendment	6/12/15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell	Division of New Drug API
Drug Product	Andrei Ponta	Division of New Drug Products I
Process	Edwin Jao	Division of Process Assessment III
Microbiology	Denise Miller	Division of Microbiology Assessment
Facility	Ebern Dobbin	Division of Inspectional Assessment
Biopharmaceutics	Okpo Eradiri	Division of Biopharmaceutics
Project/Business Process Manager	Dahlia A. Woody	RBPM Division I
Application Technical Lead	Martha Heimann	Division of New Drug Products I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	N/A	

Table of Contents

Quality Review Data Sheet

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

2. RELATED/SUPPORTING DOCUMENTS:

1. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	Adequate[2]	N/A	
	Type III)			Adequate[2]	N/A	

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[2] Previously reviewed with no new information

2. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70205	Solid oral formulations for epilepsy
IND	(b) (4)	
IND	103908	Development of iv formulation
IND	110606	Development of an oral solution in pediatric epilepsy
NDA	205836	Tablet formulation
NDA	205838	Oral solution

3. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation is pending completion of an inspection at the drug substance manufacturing facility. The inspection is scheduled for completion prior to the GRMP goal date for facility inspections. At that time, an addendum to this review containing the final recommendation will be entered into Panorama. There are no other outstanding issues that would preclude an approval recommendation.

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

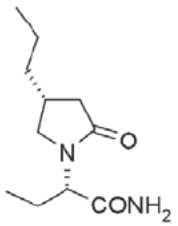
There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

II. Summary of Quality Assessments

A. Drug Substance Quality Summary for Brivaracetam

Brivaracetam [chemical name: (2S)-2-[(4R)-2-oxo-4-propyl-tetrahydro-1H-pyrrol-1-yl]butanamide] is a new chemical entity developed by the applicant, UCB Inc., for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older. The chemical structure of brivaracetam (shown below) is similar to levetiracetam, an approved, widely used, antiepileptic drug marketed by the applicant under the trade name Keppra®. The only difference between brivaracetam and levetiracetam is that levetiracetam lacks the propyl side chain at the 4-position of the lactam ring.

Chemical Structure of Brivaracetam



Brivaracetam is a neutral, small molecule that is highly soluble in aqueous media at 37°C across the physiologically relevant pH range [approximately 0.85 grams/mL at pH 1.2, pH 4.,5 and pH 7.4]. It is also highly permeable. In a radioactive mass balance study urinary excretion reached 96.8% of the brivaracetam dose.

(b) (4)

Brivaracetam is manufactured (b) (4)

Brivaracetam for parenteral use (NDA 205837) is manufactured (b) (4)

Brivaracetam drug substance is packaged in (b) (4) that comply with FDA requirements for food contact application. (b) (4)

The stability data provided in the application support a re-test period of at least (b) (4) months for oral grade brivaracetam, and at least (b) (4) months for the injectable grade material (b) (4) The re-test period for injectable grade brivaracetam may be extended based on additional data from ongoing studies.

B. Drug Product Quality Summary for Brivaracetam Injection

Brivaracetam injection (10 mg/mL) has been developed as emergency medication for epilepsy patients when oral administration is temporarily not feasible. The product is a sterile, aqueous, preservative free solution. Each mL of Brivaracetam injection also contains (b) (4) mg sodium chloride (b) (4) mg sodium acetate, and acetic acid for pH

adjustment. All excipients comply with USP/NF and Eur. Ph. compendial requirements, and are commonly used in parenteral products at (or above) the proposed levels for Brivaracetam injection.

Brivaracetam injection is supplied as single use-vials containing 50 mg brivaracetam in 5 mL of solution (10 mg/mL). The product may be administered as a bolus injection or as a 15 minute IV infusion. The product does not require dilution prior to use.

Brivaracetam injection is manufactured using conventional processes for production of sterile products. Unit operations include:

The drug product expiration dating period is 36 months when stored at controlled room temperature conditions [25ºC (77ºF); excursions 15°C to 30ºC (59°F to 86ºF)].

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Briviact is proposed
Non Proprietary Name of the Drug Product	brivaracetam injection
Non Proprietary Name of the Drug Substance	brivaracetam
Proposed Indication(s) including Intended Patient Population	Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older
Duration of Treatment	Short-term replacement therapy when oral administration is not feasible
Maximum Daily Dose	200 mg per day
Alternative Methods of Administration	Tablets and oral solution (pending NDAs)

D. Biopharmaceutics Considerations

1. BCS Classification:

A. *Drug Substance:* Brivaracetam was designated as a BCS Class 1 substance by FDA in a letter to the Applicant dated 12/21/2007.

B. *Drug Product:* The BCS is not applicable to this drug product since it is a solution.

2. Biowaivers/Biostudies

A. *Biowaiver Requests:* There is no biowaiver request to be evaluated in this Application.

B. *PK studies:* Please refer to the Clinical Pharmacology Review for the evaluation of all in-vivo BA/BE studies associated with this NDA.
C. *IVIVC:* N/A

E. Novel Approaches

The applicant did not use any novel approaches or technology in the manufacture of brivaracetam drug substance or Brivaracetam injection.

F. Any Special Product Quality Labeling Recommendations

Brivaracetam injection should not be stored frozen.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Martha R. Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
Date: 2015.08.10 19:33:11 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

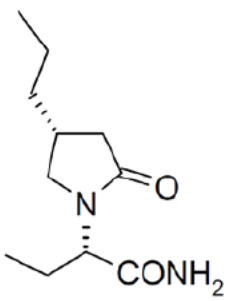
Reviewer Notes on Mechanism of Action

- Brivaracetam is a chemical relative (analog) of the anti-epilepsy drug levetiracetam. They both display high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A (SV2A). The binding affinity for brivaracetam is approximately 10-fold higher than for levetiracetam. Levetiracetam is the same structure as brivaracetam, but it lacks the propyl appendage in the 4-position of the lactam ring.
- Unlike levetiracetam, brivaracetam also reduces voltage-dependent sodium currents. It also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid- and glycine-induced currents.
- Brivaracetam is extensively metabolized, but seizure protection is linked to the parent compound.
- Significantly lower doses of brivaracetam are effective with respect to levetiracetam.
- Brivaracetam is the 2S,4R enantiomer. The 2S,4S enantiomer, also known as ucb 34713, which can be present in brivaracetam up to (b) (4)%, has approximately one third the binding affinity for SV2A as described in J. Med. Chem., **2004**, *47*, 530-549.

2.3.S.1 General Information

Applicant's Response:

Naming and Structure:
INN: Brivaracetam
Chemical Name: (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide
Code Names: ucb 34714 or BRV
Chemical Abstracts Registry Number: 357336-20-0
Figure 1–1: Structure of Brivaracetam



Molecular Formula: $C_{11}H_{20}N_2O_2$

Molecular Weight: 212.29
Stereochemistry: 2 chiral centers, with configuration (2S, 4R), drug substance is a single enantiomer, (b) (4)

General Properties
Appearance: white to off-white crystalline powder
Melting Point (range): 76.0 to 78.7°C
Solubility in Aqueous Media: ~0.85 g/mL in pH 1.2, 4.5 and 7.4 at 37°C (considered very soluble)
Permeability: Reported to be highly permeable. Radioactive mass balance study shows 96.8% of dose found by urinary excretion, 92.2% within 48 hours. High apparent permeability through passive diffusion was measured in vitro in Caco-2 cells. (b) (4)

LogP: 1.04
pKa: no ionizable centers
Not Hygroscopic
Specific Rotation (b) (4)
Polymorphism: (b) (4)

Particle Size Distribution:

I. (b) (4)

a. D(v,0.5) from (b) (4) µm
b. D(v, 0.9) not more than (b) (4) µm

Reviewer's Assessment: The API is not a salt, and is water soluble and exhibits high permeability. (b) (4) [redacted] **The API is not hygroscopic. The physical properties of this API (crystalline solid with a melting point significantly higher than ambient temperature)** (b) (4) [redacted] **These are potential degradation pathways. The risk to the patient is low due to the understanding of these potential pathways, the applicant has built in appropriate controls to limit these forms of degradation. This is discussed in the manufacturing process below.**

2.3.S.2 Manufacture

(b) (4) [redacted]

31 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
Charles F. Jewell Jr.: I recommend approval from the drug substance perspective.
7/23/2015

Supervisor Comments and Concurrence:
Kasturi Srinivasachar: I concur.
7/23/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Brivaracetam is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. The recommend Brivaracetam starting dose is 50 mg twice daily. Brivaracetam solution for injection (10 mg/mL) has been developed as emergency medication for epilepsy patients when oral administration is temporarily not feasible. The drug product is supplied as a 10 mg/mL solution in a single-use (b) (4) mL vial for perfusion and direct intravenous administration.

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

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

Brivaracetam solution for injection is a clear, colorless liquid supplied as a sterile, preservative-free solution. Each single-use vial contains 50 mg of Brivaracetam in solution, at a concentration of 10 mg/mL.

The qualitative and quantitative composition of the drug product is included below:

Component	Quality Standard	Function	Quantity (mg/mL)	Quantity per 50 mg dose (mg/5 mL)
Brivaracetam	Injectable Grade In-House	API	10.00[a]	50.00[a]
Sodium chloride	Injectable Grade USP / Ph. Eur.	(b) (4)		(b) (4)
Sodium acetate (trihydrate)	USP / Ph. Eur.			
Glacial acetic acid	USP / Ph. Eur.	pH Adjuster		
Water for injection	USP / Ph. Eur.	(b) (4)		(b) (4)

Reviewer's Assessment: Adequate

Brivaracetam solution for injection is supplied as a 10 mg/mL solution in a single-use vial. Excipients used in the formulation are common and do not present a significant safety risk from a CMC perspective. None of the excipients exceed the FDA inactive ingredient database limit for this route of administration. The formulation is preservative free.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

Components of the Drug Product

The formulation employs well-established excipients: water for injection (WFI), sodium acetate (trihydrate), glacial acetic acid, and sodium chloride.

Drug Substance

Brivaracetam is very soluble in aqueous media across the range pH 1.2 to pH 7.4 (b) (4) It is also very soluble in ethanol and acetonitrile. It is very slightly soluble in n-hexane and (b) (4). Brivaracetam is highly permeable. Brivaracetam is classified as 'Class 1' according to the BCS.

(b) (4)

Long term and accelerated stability studies under ICH conditions have been performed and demonstrate excellent stability to heat and humidity exposure of the drug substance.

Excipients

The excipients used for the manufacture of Brivaracetam solution for injection are standard pharmacopoeial excipients commonly used for the manufacture of sterile solutions. The excipients have been selected based on experience with other injectable drug products developed by UCB Pharma S.A. No preservatives are included in the formulation.

Drug Product

In aqueous solution, Brivaracetam is stable with optimum stability at pH 5.5. (b) (4)

(b) (4)

Light has no observable effect on solution stability.

The initial drug product formulation contained (b) (4)

Study	Phase	Purpose	Formulation	Strength	Batch #
N01256	I	Safety Absolute bioavailability	(b) (4)	10 mg/mL	15684
N01258	III	Safety		10 mg/mL	BX1005675 BX1005676 BX1005674
EP0007	I	Bioequivalence / bioavailability		10 mg/mL	BX1005674 BX1005676 BX1006457

Physiochemical and Biological Properties

(b) (4)

Container Closure System

Brivaracetam solution for injection is packaged in a single-use container, a Type 1 colorless glass vial closed with a (b) (4) stopper and sealed with (b) (4) cap overseal.

The container closure system ensures the microbiological integrity of the drug product. This has been demonstrated for the chosen glass vial and rubber stopper by the appropriate container closure integrity testing.

Based on a maximum daily dose of 200 mg of Brivaracetam, daily intakes (µg/day) have been calculated for leachable compounds detected after 6 months storage at 30°C / 75% RH and 40°C / 75% RH. A toxicological assessment of the data concluded that there is no toxicological concern for these compounds at the levels found.

Based on these results, the Brivaracetam solution for injection container closure system is considered suitable for the intended use.

Reviewer's Assessment: Adequate (Applicant addressed issues in the IR reply)

The applicant has developed three dosage forms: film coated tablets, an oral solution, and a solution for injection. The solution for injection is developed as an emergency medication for epilepsy patients when oral administration is temporarily not feasible.

Drug substance solubility is critical for solution for injections. This risk is minimized for the proposed drug product as Brivaracetam is a BCS Class 1 drug substance. Furthermore, excipients used in the drug product are commonly found in sterile solutions. This is acceptable.

(b) (4)

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(b) (4)

[redacted]

2.3.P.4 Control of Excipients

18. Is the quality of all excipients adequately controlled with satisfactory specifications?

Applicant's Response:

Sodium chloride, sodium acetate, glacial acetic acid and water for injection are tested according to the corresponding monographs of the Ph. Eur. and USP.

Reviewer's Assessment: Adequate

The excipients used in the drug product formulation are well established and commonly used in injections. All excipients used in the drug product are compendial grade. The applicant indicates that the excipients are tested according to the corresponding USP monographs.

2.3.P.5 Control of Drug Product

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

Applicant's Response:

Specifications

Brivaracetam Solution for Injection Specifications & Clinical Batch Results

TESTS	Acceptance Criteria	Test Method	Results BX1006457
Description	Opalescence (b) (4) Coloration (b) (4)	Ph. Eur. 2.2.1 Ph. Eur. 2.2.2	Complies Complies
Identification: HPLC Chiral HPLC	 Retention time corresponds to retention time of standard Retention time corresponds to retention time of standard	 Meth-001888 (HPLC) Meth-001448 (Chiral HPLC)	 Complies Complies

TESTS	Acceptance Criteria	Test Method	Results BX1006457
Assay Brivaracetam	(b) (4) % of label strength (10 mg/mL)	Meth-001888 (HPLC)	(b) (4)
(b) (4) Degradants: (b) (4) Any Unspecified Total of Unspecified Total Degradation Products	NMT (b) (4) % NMT % NMT % NMT %	Meth-001888 (HPLC)	
(b) (4)	NMT (b) (4) % NMT % NMT %		
pH	(b) (4)	USP <791>	
Osmolality	(b) (4) mOsmol/kg	USP <785>	
Sterility	Sterile	USP <71>	Complies
Bacterial Endotoxins	NMT (b) (4) IU/mL	USP <85> (Gel-Clot)	(b) (4)
Sub visible Particles Particles (b) (4) µm Particles (b) (4) µm	NMT (b) (4) 600 per vial	<USP 788> (Method 1)	
Extractable Volume	NLT (b) (4) mL	USP <1>	
Container Closure Integrity Test**	Sample color is not different from blank	meth-004092 (Dye ingress)	

NQ = Not Quantifiable

(b) (4)

Justification

TESTS	Justification
Description	The appearance of Brivaracetam solution for injection is examined by visual inspection. It is tested according to Ph. Eur. 2.2.1 and Ph. Eur. 2.2.2 (b) (4) .
Identification	Brivaracetam drug substance identity is confirmed at release by performing a reversed phase HPLC test and an additional normal phase chiral HPLC test.
Assay Brivaracetam	This acceptance limit is based on data from batch analyses and stability studies included in the application.
(b) (4) degradation products.	(b) (4)

TESTS	Justification
(b) (4) degradation products	(b) (4)
pH	The pH of Brivaracetam solution for injection is determined according to USP<791>. pH needs to be maintained between (b) (4) to ensure optimal product stability (b) (4)
Osmolality	The osmolality of Brivaracetam solution for injection is tested according to USP <785>. The osmolality of Brivaracetam solution for injection was determined on nine retained clinical and stability batches and is demonstrated not to be impacted by storage time.
Sterility	The sterility of Brivaracetam solution for injection is tested according to method of USP <71> (b) (4).
Bacterial Endotoxins	Bacterial endotoxins are limited to no more than (b) (4) IU/mL and are tested according to USP <85> (b) (4).
Particulate Contamination	Acceptance criteria are in line with USP <788> (Method 1).
Extractable Volume	Extractable volume is tested according to USP <1>.
Container Closure Test	Container closure integrity is verified using a reduced pressure immersion test method with a blue dye

Reviewer's Assessment: Adequate (Applicant addressed issues in the IR reply)

The acceptance criterion for description includes both opalescence and color. The applicant uses European Pharmacopeia methods for testing. This is acceptable.

Two separate HPLC methods are used to identify the drug substance, a reverse phase HPLC and a normal phase chiral HPLC method. The retention time resulting from drug product analysis must match the retention time of the standard. This is acceptable.

The reverse phase HPLC method used for identification is also used for assay testing. The assay limits are (b) (4) % of the labeled strength. This is acceptable.

The pH acceptance criterion is (b) (4) The applicant justifies this range stating, "pH needs to be maintained between (b) (4) to ensure optimal product stability (b) (4)

(b) (4)." The applicant previously indicated that (b) (4)

.

The bacterial endotoxin limit is set to no more than (b) (4) IU/mL. (b) (4) . The applicant sets the limit according to the USP monograph, as shown below.

Endotoxin Limit = K/M

K = (b) (4) IU/kg; M = maximum recommended human dose/kg body weight (200 mg)

The applicant assumes a 70 kg body weight, resulting in a (b) (4) IU/mg endotoxin limit. The drug product is at a 10 mg/mL concentration, thereby resulting in a (b) (4) IU/mL endotoxin limit. The applicant sets a more conservative limit at (b) (4) IU/mL.

The proposed specifications for sterility, extractable volume, container closure, osmolality, and particulate matter are typical for solution for injections. This is acceptable.

Impurities

The drug product manufacturing process does not generate any impurities other than those identified for the drug substance. The only (b) (4) degradation product observed at reportable levels is (b) (4) This impurity is qualified up to (b) (4)% and a no more than (b) (4)% limit (b) (4) The limit for any unspecified impurity is set to no more than 0.20%, per ICH Q3B (R2) guidelines. This is acceptable.

(b) (4)

Stability studies up to 36 months show that these impurities do not increase with time. These impurities are closely controlled in the drug substance specifications. This is acceptable.

Batch Analyses

(b) (4)

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Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: Adequate

None proposed.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The drug product data is adequate to support approval from a quality perspective.

Andrei Ponta
28- Jun-2015

Supervisor Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.; Branch Chief (Acting), Branch I, DNDP, ONDP
July 31, 2015

ASSESSMENT OF THE PROCESS

Summary of process review

The drug product is manufactured through [redacted] (b) (4) **The manufacturing process appears to be under adequate control.**

This NDA may be approved from the process perspective.

[redacted] (b) (4)

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R.2 Comparability Protocols

No comparability protocol is submitted in the original NDA and subsequent amendments under this review.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:
Approval
Edwin Jao, PhD 7/20/2015

Supervisor Comments and Concurrence: LChristensen 07/20/2015

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

30. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.
- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how the potential issues identified above, were/were not mitigated.

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		CSN	(b) (4)	*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	GMP Inspection (b) (4) 2 item 483, firms corrective and preventive actions were adequate	Acceptable

[redacted] (b) (4)		CSN	[redacted] (b) (4)	*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	Surveillance Inspection Conducted [redacted] (b) (4), No FDA 483	Acceptable
UCB Pharma Belgium	3003909356	CSN	[redacted] (b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	[redacted] (b) (4) *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	Inspection Scheduled September 2015	Pre-Approval(PAI) inspection is required

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	(b) (4)	6	6	30	42
		CSN		6	6	30	42
UCB Pharma Belgium	3003909356	CSN	*Release testing of drug substance, *Packaging of drug substance, *Stability	2	6	30	38

			testing of drug substance				

(b) (4)

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant outstanding manufacturing risks that will affect this application. Pre-approval inspection coverage is required for **UCB Pharma Belgium (FEI 3003909356),** however, there are no anticipated concerns that will possibly affect the approval of this application going into the inspection. UCB inspection is scheduled for completion by the "GRMP" date for NME NDA facility inspections and the overall facility recommendation will be made at that time.

Ebern Dobbin
Consumer Safety Officer

Supervisor Comments and Concurrence:

Concur with initial assessment, final assessment following completion of inspection activities for UCB

Mahesh Ramanadham, 8/10/15.

ASSESSMENT OF THE BIOPHARMACEUTICS

32. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

The dosage form is a solution for injection; in-vitro drug release characterization is therefore not applicable to this NDA.

33. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

There were no changes that required bridging of formulations.

Reviewer's Assessment:

There were no biopharmaceutics data to evaluate in this Application. Please refer to the Clinical Pharmacology review for assessment of the in-vivo studies that were conducted in support of this NDA.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
The Division of Biopharmaceutics defers the approvability recommendation on this NDA to the other review disciplines.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

34. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a sterile, clear, colorless liquid. It is a single use vial for intravenous injection.
- Drug product composition – The composition of the drug product was provided in Section 2.3.P.1 Table 1-1 of the application. The drug product is a non-preserved aqueous solution with a pH of 5.5.
- Description of container closure system –
  - Vial: Type 1 clear glass (b) (4) vial (b) (4)
  - Stopper: Grey 20 mm, (b) (4) rubber stopper (b) (4)

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure Integrity (CCI) – tested by both dye ingress and microbial ingress methods.

(b) (4)

(b) (4)

(b) (4)

- Preservative Effectiveness – NA, not preserved
- Justification for not having a microbial limit specification for a non-sterile drug product – NA, sterile product.

ADEQUATE

REVIEWER COMMENT – The container closure integrity studies support the ability of the CC system to maintain integrity at the time of manufacture. The integrity of the container closure system over the proposed shelf life is assessed in the stability program and is reviewed in the P.8 section of this review.

P.3 Manufacture
P.3.1 Manufacturers
P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
This is recommended for approval from a quality microbiology perspective.

Denise A. Miller, Microbiologist
OFP/DMA/Branch II
7/16/15

Supervisor Comments and Concurrence:

Neal J. Sweeney, Ph.D. 7/30/15
Acting Microbiology Quality Assessment Lead
OPQ/OPF/DMA/Branch 2

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Evaluation by Drug Product Reviewer:

38. Is the applicant's claim for categorical exclusion acceptable?
39. Is the applicant's Environmental Assessment adequate for approval of the application?
40.

Applicant's Response:

This NDA is subject to categorical exclusion under 21 CFR 25.31(b). Therefore, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

UCB certifies that, to the best of our knowledge, no extraordinary circumstances exist where the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(d).

The proposed action complies with the following categorical exclusion criterion: the Expected Introduction Concentration (EIC) for Brivaracetam in the aquatic environment is below 1 ppb.

The mathematical formula used for calculation of the EIC was that recommended in the "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" (Center for Drug Evaluation and Research, July, 1998, page 4). The calculation of the EIC is based on the highest quantity of the active moiety expected to be produced for use in any of the next five years.

Calculation of the EIC of Brivaracetam in the Aquatic Environment:

EIC–Aquatic (ppb) = A x B x C x D

Where A = kg/year production (as active moiety); B = 1/liters per day entering POTWs*; C = year/365 days; D = 109 µg/kg (conversion factor)

*1.214 x 1011 liters per day entering publicly owned treatment works (POTW's); Source: 1996 Needs Survey, Report to Congress.

The value of the parameters A, B, C and D are as follows:

A = (b) (4) kg (5th year production); B = (b) (4); C = (b) (4); D = 109 µg/kg (conversion factor)

EIC – Aquatic (ppb) = A x B x C x D = (b) (4) ppb ((b) (4) ppb)

Conclusion - the EIC of Brivaracetam in the aquatic environment is < 1 ppb. Based on the EIC, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

I. Review of Common Technical Document-Quality (CTD-Q) Module 1

Evaluation by Drug Product Reviewer:

Labeling & Package Insert

I. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Item	Information Provided in NDA		Reviewer's Assessment
Product title, Drug name (201.57(a)(2))			
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		The proposed proprietary name is Briviact.
Dosage form, route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Controlled drug substance symbol (if applicable)	NA		NA
Dosage Forms and Strengths (201.57(a)(8))			
A concise summary of dosage forms and strengths	Brivaracetam drug products are available as film coated tablets, an oral solution, and a solution for injection. Immediate release tablets containing 10 mg, 25 mg, 50 mg, 75 mg and 100 mg of Brivaracetam have been developed. The oral solution contains 10 mg/mL of Brivaracetam. Brivaracetam solution for injection is provided in a single-use vail containing 50 mg of Brivaracetam in 5 mL of solution (10 mg/mL).		**The label and information provided in NDA are in agreement. However, the applicant does not provide subheadings (e.g., injectable, capsule).**

NA = Not Applicable

Conclusion:

The label is accurate and consistent with the information provided in the NDA. However, the label does not include subheadings per CFR 201.57(a)(8).

Information to be Requested

- Adequate subheadings are not included in the package insert highlights section, under the dosage forms and strengths portion. CFR 201.57(a)(8) requires a concise summary with "any appropriate subheadings (e.g., tablets, capsules, injectable, suspension)." Differentiate between the oral solution and the solution for injection. Specifically, indicate that the single-use vial is to be used for injection.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA			Reviewer's Assessment
Available dosage forms	Tablets	Oral Solution	Solution for Injection	The label and information provided in NDA are in agreement.
Strengths: in metric system	10 mg; 25 mg; 50 mg; 75 mg; and 100 mg	10 mg/mL	50 mg/ 5 mL	The label and information provided in NDA are in agreement.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face • 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution			The label and information provided in NDA are in agreement.

Conclusion:

The label is accurate and consistent with the information provided in the NDA.

#11: Description (21CFR 201.57(c)(12))

(b) (4)

Item	Information Provided in NDA		Reviewer's Assessment
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		Briviact is the proposed proprietary name.
Dosage form and route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Active moiety expression of strength with equivalence statement for salt (if applicable)	NA		NA
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tablets Tablets contain sodium croscarmellose, lactose monohydrate, betadex (β-cyclodextrin), anhydrous lactose, and magnesium stearate. Tablets are coated with the following materials: 10 mg tablets - polyvinyl alcohol, talc,		The label and information provided in NDA are in agreement.

	polyethylene glycol 3350, titanium dioxide 25 mg and 100 mg tablets - polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, black iron oxide 50 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide 75 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide, black iron oxide Oral Solution It contains: sodium citrate, anhydrous citric acid, methylparaben, sodium carboxymethylcellulose, sucralose, sorbitol solution, glycerin, raspberry flavor, and purified water. Solution for Injection It contains: sodium acetate (trihydrate), glacial acetic acid (for pH adjustment to 5.5), sodium chloride and water for injection.	
Statement of being sterile (if applicable)	Brivaracetam solution for injection is supplied as a clear, colorless liquid supplied as a sterile, preservative-free solution.	The label and information provided in NDA are in agreement.
Pharmacological/ therapeutic class	Antiepileptic	**The label is missing this information.**
Chemical name, structural formula, molecular weight	The chemical name is (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide. Its molecular formula is $C_{11}H_{20}N_2O_2$ and its molecular weight is 212.29.	The label and information provided in NDA are in agreement.
Radioactivity	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Brivaracetam, a white to off-white crystalline powder, is very soluble in aqueous media across the range pH 1.2 to pH 7.4 (b) (4) It is also very soluble in ethanol and freely soluble in acetonitrile. It is very slightly soluble in n-hexane (b) (4). Brivaracetam is a chiral molecule. (b) (4)	The label and information provided in NDA are in agreement.

Conclusion:

The label contains the placeholder "TRADENAME" for the proprietary name. The applicant has proposed Briviact as the proprietary name for Brivaracetam.

(b) (4) However, this is not required under 21CFR 201.57(c)(12).

The therapeutic class information is missing under the description heading. The applicant will be asked to update the label accordingly. The remaining label information is accurate and consistent with the information provided in the NDA.

Information to be Requested

- Information regarding the pharmaceutical/therapeutic class is absent in the package insert description section (#11). According to CFR 201.57(c)(12), the description section must contain the pharmacological or therapeutic class of the drug. Update the label with the appropriate information.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 **HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied

(b) (4)

16.2 Storage

Store at 25 °C (77 °F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not freeze TRADENAME injection or oral solution.

Discard any unused TRADENAME oral solution remaining after 5 months of first opening the bottle.

Item	Information Provided in NDA		Reviewer's Assessment
Strength of dosage form	Strength:	Dosage Form:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Available units (e.g., bottles of 100 tablets)	Tablets: 35 cc (10 mg, 25 mg and 50 mg) and 60 cc (75 mg and 100 mg) bottles (60 tablet count) Oral Solution: 300 mL bottle Solution for Injection: (b) (4) mL single-use vial		The label and information provided in NDA are in agreement.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet		There is currently a placeholder for the NDC-number. The label and information provided in

	debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face • 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution	NDA are in agreement.
Special handling (e.g., protect from light, do not freeze)	The drug product is stable to short term excursions between (b) (4)	The label includes the additional instructions "do not freeze" for the oral solution and solution for injection drug product.
Storage conditions	Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	The label and information provided in NDA are in agreement.

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

TRADENAME Tablets, TRADENAME Oral Solution, and TRADENAME Injection manufactured for
UCB, Inc.
Smyrna, GA 30080

TRADENAME is a registered trademark of the UCB Group of Companies
© 20XX, UCB, Inc., Smyrna, GA 30080
All rights reserved.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	UCB Pharma S.A.	The label and information provided in NDA are in agreement.

Conclusion:

The label includes the special handling instructions, "do not freeze" for the oral solution and solution for injection. This is acceptable.

The label is accurate and consistent with the information provided in the NDA.

II. Labels

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The net quantity of contents in terms of fluid measure (mL) is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The label bears the "Rx only" statement.	Adequate
Storage (not required)	NA	NA
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the label.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
Others	NA	NA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The vial label is accurate and consistent with the information provided in the NDA. All CFR requirements are met.

III. Cartons

(b) (4)

[redacted]

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The net quantity of contents in terms of fluid measure (mL) is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables) [201.10(a), 21CFR201.100 (b) (5) (iii)]	The solution for injection contains: sodium acetate (trihydrate), glacial acetic acid (for pH adjustment to 5.5), sodium chloride and water for injection.	Adequate – All ingredients are added to adjust the pH or to make the drug isotonic.
Sterility Information (if applicable)	(b) (4)	**Inadequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	The carton bears the "Rx only" statement.	Adequate
Storage Conditions	Store at controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]. Do not freeze.	Information is consistent with other labeling.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the top left section of the package. However, it is not preceded by the prefix "NDC."	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate

Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	A "See package insert for dosage information" statement is included on the side of the package.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	There is no "Keep out of reach of children" statement.	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	The route of administration is included in the label.	Adequate

Conclusion:

The solution for injection carton is accurate and consistent with the information provided in the NDA. However, there is no sterility information provided.

Information to be Requested

- Update the solution for injection carton accordingly to include information regarding the drug product sterility.

II. List of Deficiencies To Be Communicated

There are no deficiencies to be communicated at this time.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

(b) (4)

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterility	Process parameters, container, formulation	M	(b) (4)	Acceptable	
Endotoxin, pyrogen	Process parameters, container, formulation	M			
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	L	N/A		
Fill Volume/ deliverable volume	Formulation, process parameters, container closure	L	N/A		
Osmolality	Formulation, raw materials	L	N/A		
pH (High)	Formulation, raw materials, process parameters, container closure	L	N/A		
pH (Low)	Formulation, raw materials, process parameters, container closure	L	N/A		
Particulate matter	Formulation, raw materials, process parameters, container closure	M	(b) (4)		
Leachable extractables	Formulation, raw materials, process parameters, container closure	L	N/A		
Appearance	Formulation, raw materials, process parameters, container closure	L	N/A		

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

NDA 205838
Review # 1

Drug Name/Dosage Form	Brivaracetam Oral Solution
Strength	10 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	UCB Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Quality Amendments	12/22/14
Quality Amendments	1/12/15
Quality Amendments	3/10/15
Quality Amendments	5/20/15
Quality Amendments	6/17/15

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell	Division of New Drug API
Drug Product	Andrei Ponta	Division of New Drug Products I
Process	Edwin Jao Denise Miller	Division of Process Assessment III Division of Microbiology Assessment
Microbiology	Denise Miller	Division of Microbiology Assessment
Facility	Ebern Dobbin	Division of Inspectional Assessment
Biopharmaceutics	Okpo Eradiri	Division of Biopharmaceutics
Project/Business Process Manager	Dahlia A. Woody	RBPM Division I
Application Technical Lead	Martha Heimann	Division of New Drug Products I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment	N/A	

Table of Contents

Quality Review Data Sheet

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

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A		
	Type III			Adequate[2]		
	Type IV			Adequate[2]		

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[2] Previously reviewed with no new information
[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70205	Solid oral formulations for epilepsy
IND	(b) (4)	(b) (4)
IND	103908	Development of iv formulation
IND	110606	Development of an oral solution in pediatric epilepsy
NDA	205836	Tablet formulation
NDA	205837	IV formulation

a) CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation is pending completion of an inspection at the drug substance manufacturing facility. The inspection is scheduled for completion prior to the GRMP goal date for facility inspections. At that time, an addendum to this review containing the final recommendation will be entered into Panorama. There are no other outstanding issues that would preclude an approval recommendation.

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

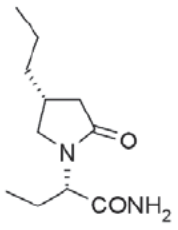
There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

II. Summary of Quality Assessments

A. Drug Substance Quality Summary for Brivaracetam

Brivaracetam [chemical name: (2S)-2-[(4R)-2-oxo-4-propyl-tetrahydro-1H-pyrrol-1-yl]butanamide] is a new chemical entity developed by the applicant, UCB Inc., for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older. The chemical structure of brivaracetam (shown below) is similar to levetiracetam, an approved, widely used, antiepileptic drug marketed by the applicant under the trade name Keppra®. The only difference between brivaracetam and levetiracetam is that levetiracetam lacks the propyl side chain at the 4-position of the lactam ring.

Chemical Structure of Brivaracetam



Brivaracetam is a neutral, small molecule that is highly soluble in aqueous media at 37°C across the physiologically relevant pH range [approximately 0.85 grams/mL at pH 1.2, pH 4.,5 and pH 7.4]. It is also highly permeable. In a radioactive mass balance study urinary excretion reached 96.8% of the brivaracetam dose.

(b) (4)

Brivaracetam is manufactured (b) (4)

Brivaracetam for parenteral use (NDA 205837) is manufactured (b) (4)

Brivaracetam drug substance is packaged in (b) (4) that comply with FDA requirements for food contact application. (b) (4)

The stability data provided in the application support a re-test period of at least (b) (4) months for oral grade brivaracetam, and at least (b) (4) months for the injectable grade material at controlled room temperature. The re-test period for injectable grade brivaracetam may be extended based on additional data from ongoing studies.

B. Drug Product Quality Summary for Brivaracetam Oral Solution

Brivaracetam oral solution has been developed for patients with difficulty swallowing. The product is a slightly viscous, clear, colorless to yellowish liquid solution containing 10 mg/mL of Brivaracetam and the following inactive

ingredients: methylparaben, anhydrous acetic acid, sodium citrate, carboxymethylcellulose sodium, sucralose, sorbitol solution, glycerin, and raspberry flavor. All excipients except the raspberry flavor comply with USP/NF compendial requirements, and are commonly used in oral dosage forms at (or above) the proposed levels for Brivaracetam oral solution.

Brivaracetam oral solution is contained in a 300 mL, type III amber glass bottle with (b) (4) The applicant indicates that dispensing devices (e.g., oral syringe, bottle adapter, etc.) will not be supplied with the product.

The manufacturing process Brivaracetam oral solution is relatively straightforward. (b) (4)

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Briviact is proposed
Non Proprietary Name of the Drug Product	brivaracetam oral solution
Non Proprietary Name of the Drug Substance	Brivaracetam
Proposed Indication(s) including Intended Patient Population	Adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older
Duration of Treatment	Chronic
Maximum Daily Dose	200 mg per day
Alternative Methods of Administration	Tablets and IV injection (pending NDAs)

D. Biopharmaceutics Considerations

1. BCS Classification:
   - *Drug Substance:* Brivaracetam was designated as a BCS Class 1 substance by FDA in a letter to the Applicant dated 12/21/2007.
   - *Drug Product:* The BCS is not applicable to this drug product since it is a solution.

2. Biowaivers/Biostudies
    - *Biowaiver Requests:* There is no biowaiver request to be evaluated in this Application.
    - *PK studies:* Please refer to the Clinical Pharmacology Review for the evaluation of all in-vivo PK studies associated with this NDA.
    - *IVIVC:* N/A

E. Novel Approaches

The applicant did not use any novel approaches or technology in the manufacture of brivaracetam drug substance or Brivaracetam injection.

F. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Martha R. Heimann -S

Digitally signed by Martha R. Heimann -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300091527, cn=Martha R. Heimann -S
Date: 2015.08.10 19:42:52 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

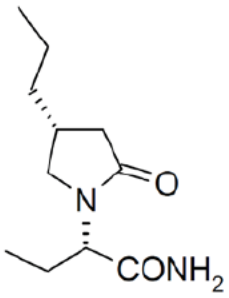
Reviewer Notes on Mechanism of Action

- Brivaracetam is a chemical relative (analog) of the anti-epilepsy drug levetiracetam. They both display high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A (SV2A). The binding affinity for brivaracetam is approximately 10-fold higher than for levetiracetam. Levetiracetam is the same structure as brivaracetam, but it lacks the propyl appendage in the 4-position of the lactam ring.
- Unlike levetiracetam, brivaracetam also reduces voltage-dependent sodium currents. It also reverses the inhibitory effects of negative allosteric modulators on gamma-aminobutyric acid- and glycine-induced currents.
- Brivaracetam is extensively metabolized, but seizure protection is linked to the parent compound.
- Significantly lower doses of brivaracetam are effective with respect to levetiracetam.
- Brivaracetam is the 2S,4R enantiomer. The 2S,4S enantiomer, also known as ucb 34713, which can be present in brivaracetam up to (b) (4) %, has approximately one third the binding affinity for SV2A as described in J. Med. Chem., **2004**, *47*, 530-549.

2.3.S.1 General Information

Applicant's Response:

Naming and Structure:
INN: Brivaracetam
Chemical Name: (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide
Code Names: ucb 34714 or BRV
Chemical Abstracts Registry Number: 357336-20-0
Figure 1–1: Structure of Brivaracetam



Molecular Formula: $C_{11}H_{20}N_2O_2$

Molecular Weight: 212.29
Stereochemistry: 2 chiral centers, with configuration (2S, 4R), drug substance is a single enantiomer (b) (4)

General Properties
Appearance: white to off-white crystalline powder
Melting Point (range): 76.0 to 78.7°C
Solubility in Aqueous Media: ~0.85 g/mL in pH 1.2, 4.5 and 7.4 at 37°C (considered very soluble)
Permeability: Reported to be highly permeable. Radioactive mass balance study shows 96.8% of dose found by urinary excretion, 92.2% within 48 hours. High apparent permeability through passive diffusion was measured in vitro in Caco-2 cells. (b) (4) .
LogP: 1.04
pKa: no ionizable centers
Not Hygroscopic
Specific Rotation (b) (4)
Polymorphism:
(b) (4)

Particle Size Distribution:

- final stage of production includes a de-lumping / milling process targeting
  - D(v,0.5) from (b) (4) µm
  - D(v, 0.9) not more than (b) (4) µm

Reviewer's Assessment: The API is not a salt, and is water soluble and exhibits high permeability. (b) (4) **The API is not hygroscopic. The physical properties of this API (crystalline solid with a melting point significantly higher than ambient temperature)** (b) (4) **These are potential degradation pathways. The risk to the patient is low due to the understanding of these potential pathways, the applicant has built in appropriate controls to limit these forms of degradation. This is discussed in the manufacturing process below.**

2.3.S.2 Manufacture

(b) (4)

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Reviewer Comments: See comments on reviewer analysis of the stability data in the stability data summary section above.

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
Charles F. Jewell Jr. - I recommend approval from the perspective of drug substance.
7/23/2015

Supervisor Comments and Concurrence:
Kasturi Srinivasachar - I concur
7/23/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Brivaracetam is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. The recommend Brivaracetam starting dose is 50 mg twice daily. Brivaracetam oral solution (10 mg/mL) has been developed for patients with difficulty swallowing. The oral solution is supplied in a 300 mL bottle.

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

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Brivaracetam oral solution is a slightly viscous, clear, colorless to yellowish liquid solution containing Brivaracetam (10 mg/mL) in a 300 mL type III amber glass bottle with a polypropylene closure.

Component	Quality Standard	Function	Quantity (mg/mL)	Quantity per 50 mg dose (mg/5 mL)
Brivaracetam	Oral grade In house	API	10.00[a]	50.00[a]
Methylparaben (b) (4)	NF / Ph. Eur.	(b) (4)		(b) (4)
Anhydrous citric acid	USP / Ph. Eur.			
Sodium citrate	USP / Ph. Eur.			
Carboxymethylcellulose sodium/ (b) (4)	NF / Ph. Eur.			
Sucralose	NF / Ph. Eur.			
Sorbitol solution (b) (4) (b) (4)	USP / Ph. Eur.			
Glycerin/ (b) (4)	USP / Ph. Eur.			
Raspberry flavor (b) (4)	In house			
Purified water	USP / Ph. Eur.			
(b) (4)				

Reviewer's Assessment: Adequate

Brivaracetam oral solution is provided in 300 mL bottles at a 10 mg/mL concentration. The drug product is composed of the drug substance, various USP/NF excipients, and raspberry flavoring.

Component	% w/w *	MDD (mg)	IIG Limit
Methylparaben	(b) (4)		
Anhydrous citric acid			
Sodium citrate			

Carboxymethylcellulose sodium	(b) (4)
Sucralose	
Sorbitol solution	
Glycerin	
Raspberry flavor	

(b) (4) based on executed batch records.

(b) (4) exceeds the FDA inactive ingredient database limit for oral solutions. However, (b) (4) is approved a (b) (4)% in an oral suspension. There is minimal risk with this excipient.

The composition by w/w percent herein is calculated based on the executed batch record information.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

Components of the Drug Product

Brivaracetam oral solution contains methylparaben (b) (4), anhydrous citric acid, sodium citrate, carboxymethylcellulose sodium/ (b) (4) glycerin (b) (4) sucralose, sorbitol solution/ (b) (4) artificial raspberry flavor, and purified water.

Drug Substance

Brivaracetam oral solution is manufactured using oral grade Brivaracetam. (b) (4)

Brivaracetam is very soluble in aqueous media across the range pH 1.2 to pH 7.4 (b) (4) It is also very soluble in ethanol and acetonitrile. It is very slightly soluble in n-hexane and other non-polar solvents. Brivaracetam is highly permeable. Brivaracetam is classified as 'Class 1' according to the BCS.

(b) (4)

Long term and accelerated stability studies under ICH conditions have been performed and demonstrate excellent stability to heat and humidity exposure of the drug substance.

Excipients

The excipients utilized for the manufacture of Brivaracetam oral solution are standard pharmacopeial excipients commonly used for the manufacture of oral liquid formulations. The excipients have been selected based on experience with other oral liquid drug products developed by UCB Pharma S.A.

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Reviewer's Assessment: Adequate

None proposed.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:

The drug product data is adequate to support approval from a quality perspective.

Andrei Ponta
28- Jun-2015

Supervisor Comments and Concurrence: I concur.

Wendy I. Wilson-Lee, Ph.D.; Branch Chief (Acting), Branch I, DNDP, ONDP
July 31, 2015

ASSESSMENT OF THE PROCESS

Summary of process review

The drug product is manufactured through a process including (b) (4) **The manufacturing process is provided in sufficient details, with acceptable in-process controls. The adequacy of the manufacturing process parameters is confirmed with several full production scale batches. The actual yields for unit and total production are acceptable for all three registration batches, with good batch-to-batch consistency. The manufacturing process appears to be under adequate control.**

This NDA may be approved from the process perspective.

Review history

(b) (4)

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Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:
approval
Edwin Jao, PhD 7/22/2015

Supervisor Comments and Concurrence: LChristensen 07/23/2015

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

30. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Points to consider

- Who manufactures the drug substance? List each participant and facility involved in drug substance manufacturing/testing activities and clearly state their function. List the date of the last FDA inspection for each facility involved and the result of the inspection. Identify any historical inspectional findings that could impact the manufacturing of this product?
- For each of the facilities listed above, identify any potential GMP-related issues (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc)?
- For each of the facilities listed above, are there any indicators that warrant a pre-approval inspection? Explain why or why not.
- For each of the facilities in which a pre-approval inspection was performed, list the date performed, summary of the inspection and any un-resolved observations. Indicate how the potential issues identified above, were/were not mitigated.

Facility Name	FEI Number	Profile Code	Responsibility	Initial Risks Identified	Current Status	Final Recommendation
[redacted]	(b) (4)	CSN	(b) (4)	*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME,	GMP Inspection (b) (4), 2 item 483, firms corrective and preventive actions were adequate	Acceptable

				however this is a low risk process		
[redacted] (b) (4)		CSN	[redacted] (b) (4)	*None Identified Low Risk Process *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this is a low risk process	Surveillance Inspection Conducted [redacted] (b) (4), No FDA 483	Acceptable
UCB Pharma Belgium	3003909356	CSN	[redacted] (b) (4), *Release testing of	[redacted] (b) (4) *Product sub-score and overall initial facility risk showed up as red only because the product for this application is classified as an NME, however this	Inspection Scheduled September 2015	Pre-Approval(PAI) inspection is required

			drug substance, *Packaging of drug substance, *Stability testing of drug substance	is a low risk process		

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Initial Facility Risk Assessment for the sites involved in drug substance manufacturing:

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)		CSN	(b) (4)	6	6	30	42
		CSN		6	6	30	42

			(b) (4)				
UCB Pharma Belgium	**3003909356**	**CSN**	(b) (4) *Release testing of drug substance, *Packaging of drug substance, *Stability testing of drug substance	2	6	30	**38**

(b) (4)

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Following a review of the application and inspectional documents, there are no significant outstanding manufacturing risks that will affect this application. Pre-approval inspection coverage is required for **UCB Pharma (FEI 3003909356)** however, there are no anticipated concerns that will possibly affect the approval of this application going into the inspection. The pending UCB inspection is scheduled for completion by the "GRMP" date for NME NDA facility inspections and the overall facility recommendation will be made at that time.

Ebern Dobbin
Consumer Safety Officer, OPQ/OPF/DIA/IABII

Supervisor Comments and Concurrence:

Concur with initial assessment, final assessment following completion of inspection activities for UCB and Anabiotec

Mahesh Ramanadham, 8/10/15.

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE BIOPHARMACEUTICS

32. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

The dosage form is an Oral Solution; in-vitro drug release characterization is therefore unnecessary.

33. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

There were no changes that required bridging of formulations.

Reviewer's Assessment:

There were no biopharmaceutics data to evaluate in this Application. Please refer to the Clinical Pharmacology review for assessment of the in-vivo studies that were conducted in support of this NDA.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:
The Division of Biopharmaceutics defers the approvability recommendation on this NDA to the other review disciplines.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

34. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

This is a liquid oral drug product to be used as an adjunct therapy in the treatment of partial onset of seizures in patients 16 years of age and older with epilepsy. The proposed release specifications include testing for Total Aerobic Microbial Count (TAMC), Total Yeast and Mold Count (TYMC), and absence of *Escherichia coli* and *Salmonella* species. The proposed specifications are NMT (b) (4) cfu/mL for TAMC and NMT (b) (4) cfu/mL for TYMC. The testing methods are per USP <61> and <62> and the proposed specifications are within the recommendations of USP <1111> for an oral aqueous dosage form. The test for the absence of (b) (4) (b) (4) was not included; as this is an aqueous formulation, this testing is recommended.

An information request that was included in the 74 day letter requested the method suitability information for the microbial limits testing and that the sponsor includes a test for the absence of (b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reviewer's Assessment: There are no materials of biological origin or derived from biological sources.

37. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: The application is recommended for approval from a quality microbiology perspective.

Denise A. Miller
Microbiologist, OPF/DMA/Branch II
07/28/15

Supervisor Comments and Concurrence:

Neal J. Sweeney, Ph.D. 7/30/15
Acting Microbiology Quality Assessment Lead
OPQ/OPF/DMA/Branch 2

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

EVALUATION BY DRUG PRODUCT REVIEWER:

38. Is the applicant's claim for categorical exclusion acceptable?

39. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

This NDA is subject to categorical exclusion under 21 CFR 25.31(b). Therefore, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

UCB certifies that, to the best of our knowledge, no extraordinary circumstances exist where the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(d)).

The proposed action complies with the following categorical exclusion criterion: the Expected Introduction Concentration (EIC) for Brivaracetam in the aquatic environment is below 1 ppb.

The mathematical formula used for calculation of the EIC was that recommended in the "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications" (Center for Drug Evaluation and Research, July, 1998, page 4). The calculation of the EIC is based on the highest quantity of the active moiety expected to be produced for use in any of the next five years.

Calculation of the EIC of Brivaracetam in the Aquatic Environment:

EIC–Aquatic (ppb) = A x B x C x D

Where A = kg/year production (as active moiety); B = 1/liters per day entering POTWs*; C = year/365 days; D = 109 µg/kg (conversion factor)

*1.214 x 1011 liters per day entering publicly owned treatment works (POTW's); Source: 1996 Needs Survey, Report to Congress.

The value of the parameters A, B, C and D are as follows:

A = (b) (4) kg (5th year production); B = (b) (4); C = (b) (4); D = 109 µg/kg (conversion factor)

EIC – Aquatic (ppb) = A x B x C x D = (b) (4) ppb (b) (4) ppb)

Conclusion - the EIC of Brivaracetam in the aquatic environment is < 1 ppb. Based on the EIC, the NDA is not required to include an Environmental Assessment for Brivaracetam under 21 CFR 25.15(a).

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

I. Review of Common Technical Document-Quality (CTD-Q) Module 1

Labeling & Package Insert

EVALUATION BY DRUG PRODUCT REVIEWER:

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(b) (4)

[redacted]

Item	Information Provided in NDA		Reviewer's Assessment
Product title, Drug name (201.57(a)(2))			
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		The proposed proprietary name is Briviact.
Dosage form, route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Controlled drug substance symbol (if applicable)	NA		NA
Dosage Forms and Strengths (201.57(a)(8))			
A concise summary of dosage forms and strengths	Brivaracetam drug products are available as film coated tablets, an oral solution, and a solution for injection. Immediate release tablets containing 10 mg, 25 mg, 50 mg, 75 mg and 100 mg of Brivaracetam have been developed. The oral solution contains 10 mg/mL of		**The label and information provided in NDA are in agreement. However, the applicant does not provide subheadings (e.g., injectable, capsule).**

	Brivaracetam. Brivaracetam solution for injection is provided in a single-use vail containing 50 mg of Brivaracetam in 5 mL of solution (10 mg/mL).	

NA = Not Applicable

Conclusion:

The label is accurate and consistent with the information provided in the NDA. However, the label does not include subheadings per CFR 201.57(a)(8).

Information to be Requested

1. Adequate subheadings are not included in the package insert highlights section, under the dosage forms and strengths portion. CFR 201.57(a)(8) requires a concise summary with "any appropriate subheadings (e.g., tablets, capsules, injectable, suspension)." Differentiate between the oral solution and the solution for injection. Specifically, indicate that the single-use vial is to be used for injection.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA			Reviewer's Assessment
Available dosage forms	Tablets	Oral Solution	Solution for Injection	The label and information provided in NDA are in agreement.
Strengths: in metric system	10 mg; 25 mg; 50 mg; 75 mg; and 100 mg	10 mg/mL	50 mg/ 5 mL	The label and information provided in NDA are in agreement.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face • 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid			The label and information provided in NDA are in agreement.

	Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution	

Conclusion:

The label is accurate and consistent with the information provided in the NDA.

#11: Description (21CFR 201.57(c)(12))

(b) (4)

[redacted]

Item	Information Provided in NDA		Reviewer's Assessment
Proprietary name and established name	Proprietary: Briviact Established Name: Brivaracetam		Briviact is the proposed proprietary name.
Dosage form and route of administration	Dosage:	Route:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Active moiety expression of strength with equivalence statement	NA		NA

for salt (if applicable)		
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tablets Tablets contain sodium croscarmellose, lactose monohydrate, betadex (β-cyclodextrin), anhydrous lactose, and magnesium stearate. Tablets are coated with the following materials: 10 mg tablets - polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide 25 mg and 100 mg tablets - polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, black iron oxide 50 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide 75 mg tablets: polyvinyl alcohol, talc, polyethylene glycol 3350, titanium dioxide, yellow iron oxide, red iron oxide, black iron oxide Oral Solution It contains: sodium citrate, anhydrous citric acid, methylparaben, sodium carboxymethylcellulose, sucralose, sorbitol solution, glycerin, raspberry flavor, and purified water. Solution for Injection It contains: sodium acetate (trihydrate), glacial acetic acid (for pH adjustment to 5.5), sodium chloride and water for injection	The label and information provided in NDA are in agreement.
Statement of being sterile (if applicable)	Brivaracetam solution for injection is supplied as a clear, colorless liquid supplied as a sterile, preservative-free solution.	The label and information provided in NDA are in agreement.
Pharmacological/ therapeutic class	Antiepileptic	**The label is missing this information.**
Chemical name, structural formula, molecular weight	The chemical name is (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl] butanamide. Its molecular formula is $C_{11}H_{20}N_2O_2$ and its molecular weight is 212.29.	The label and information provided in NDA are in agreement.
Radioactivity	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	Brivaracetam, a white to off-white crystalline powder, is very soluble in aqueous media across the range pH 1.2 to pH 7.4 (b) (4) It is also very soluble in ethanol and freely soluble in acetonitrile. It is very slightly soluble in n-hexane (b) (4) Brivaracetam is a chiral molecule. (b) (4)	The label and information provided in NDA are in agreement.

Conclusion:

The label contains the placeholder "TRADENAME" for the proprietary name. The applicant has proposed Briviact as the proprietary name for Brivaracetam.

(b) (4)

However, this is not required under 21CFR 201.57(c)(12).

The therapeutic class information is missing under the description heading. The applicant will be asked to update the label accordingly. The remaining label information is accurate and consistent with the information provided in the NDA.

Information to be Requested

2. Information regarding the pharmaceutical/therapeutic class is absent in the package insert description section (#11). According to CFR 201.57(c)(12), the description section must contain the pharmacological or therapeutic class of the drug. Please update the label with the appropriate information.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 **HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied

(b) (4)

[redacted]

16.2 Storage

Store at 25 °C (77 °F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Do not freeze TRADENAME injection or oral solution.

Discard any unused TRADENAME oral solution remaining after 5 months of first opening the bottle.

Item	Information Provided in NDA		Reviewer's Assessment
Strength of dosage form	Strength:	Dosage Form:	The label and information provided in NDA are in agreement.
	10 mg; 25 mg; 50mg; 75 mg; and 100 mg	Oral Tablets	
	10 mg/mL	Oral Solution	
	50 mg/ 5 mL	Injection for Intravenous Use	
Available units (e.g., bottles of 100 tablets)	Tablets: 35 cc (10 mg, 25 mg and 50 mg) and 60 cc (75 mg and 100 mg) bottles (60 tablet count) Oral Solution: 300 mL bottle Solution for Injection: (b) (4) mL single-use vial		The label and information provided in NDA are in agreement.

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablets • 10 mg tablet - White to off-white round film-coated tablet debossed with "u10" on one face • 25 mg tablet - Grey oval film-coated tablet debossed with "u25" on one face • 50 mg tablet - Yellow oval film-coated tablet debossed with "u50" on one face • 75 mg tablet - Purple oval film-coated tablet debossed with "u75" on one face • 100 mg tablet - Green-grey oval film-coated tablet debossed with "u100" on one face Oral Solution • Slightly viscous, clear, colorless to yellowish liquid Solution for Injection • Clear, colorless liquid supplied as a sterile, preservative-free solution	There is currently a placeholder for the NDC-number. The label and information provided in NDA are in agreement.
Special handling (e.g., protect from light, do not freeze)	The drug product is stable to short term excursions between (b) (4)	The label includes the additional instructions "do not freeze" for the oral solution and solution for injection drug product.
Storage conditions	Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	The label and information provided in NDA are in agreement.

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

TRADENAME Tablets, TRADENAME Oral Solution, and TRADENAME Injection manufactured for UCB, Inc.
Smyrna, GA 30080

TRADENAME is a registered trademark of the UCB Group of Companies
© 20XX, UCB, Inc., Smyrna, GA 30080
All rights reserved.

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	UCB Pharma S.A.	The label and information provided in NDA are in agreement.

Conclusion:

The label includes the special handling instructions, "do not freeze" for the oral solution and solution for injection. This is acceptable.

The label is accurate and consistent with the information provided in the NDA.

3. Labels

1) Immediate Container Label

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The net quantity of contents in terms of fluid measure (mL) is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The label bears the "Rx only" statement.	Adequate
Storage (not required)	The label has the following storage conditions instructions: Controlled room temperature conditions [25°C (77°F); excursions 15 – 30°C (59 – 86°F)]	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	The NDC number is present on the label.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
Others	NA	NA

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The label is accurate and consistent with the information provided in the NDA. All CFR requirements are met.

2) Cartons

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name follows the proprietary name. The font size of the established name is at least half of the most prominent proprietary name font size.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The quantity of the active ingredient provided is accurate.	Adequate
Net contents (21 CFR 201.51(a))	The net quantity of contents in terms of fluid measure (mL) is included on the label.	Adequate
Lot number per 21 CFR 201.18	There is a designated space for the lot number.	Adequate
Expiration date per 21 CFR 201.17	There is a designated space for the expiration date.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	The drug product is an oral solution.	Adequate
Sterility Information (if applicable)	NA	NA
"Rx only" statement per 21 CFR 201.100(b)(1)	The carton bears the "Rx only" statement.	Adequate
Storage Conditions	The label has the following storage conditions instructions: Controlled room temperature conditions [25ºC (77ºF); excursions 15 – 30ºC (59 – 86ºF)]. Do not freeze.	Adequate
NDC number (per 21 CFR 201.2)	The NDC number is present on the top left section	Adequate

(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	of the package.	
Bar Code per 21 CFR 201.25(c)(2)**	The bar code appears on the label.	Adequate
Name of manufacturer/distributor	The manufacture UCB Inc. is listed on the label.	Adequate
"See package insert for dosage information" (21 CFR 201.55)	A "See accompanying prescribing information" statement is included on the side of the package.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	The cartons contain a "Keep out of reach of children" statement. This statement is not included on the cartons for the bottles.	Adequate
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	The route of administration is included in the label.	Adequate

Conclusion:

The oral solution carton is accurate and consistent with the information provided in the NDA. All CFR requirements are met.

II. List of Deficiencies To Be Communicated

A. Drug Substance
B. Drug Product
C. Process/Facility
D. Biopharmaceutics
E. Microbiology
F. Label/Labeling

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

B. Lifecycle Knowledge Management

a) Drug Substance

(b) (4)

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	L	Extensive (b) (4) long term stability for commercial scale product batches, in the proposed packaging	Acceptable	
Dosing accuracy	Formulation, process parameters, container closure, dosing device	M	The firm has demonstrated compatibility of the product formulation with commercially available dosing devices that measure the lowest recommended with acceptable accuracy.	Acceptable	(b) (4)
Palatability	Formulation, excipient	M	(b) (4)	Acceptable	
Leachable extractables	Formulation, raw materials, process parameters, container closure	L	Use of materials suitable for food contact and leachables studies that show no impact on product quality	Acceptable	
Appearance	Formulation, raw materials, process parameters, container closure	L	No significant changes observed in stability studies.	Acceptable	

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Comment
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	3	2	3	18	(b) (4)
Physical stability (solid state)	Formulation, process parameters, moisture	3 (+1) = 4	2	4	32	
Content uniformity	Low dose, particle size/shape, segregation, flow property	3 (-1) = 2	3	4	24	
Microbial limits	Formulation, raw materials, process parameters, moisture	1	2	5	10	
Dissolution	Particle size, moisture, hardness, size, shape, film coat	3	2	2	12	

Martha R. Heimann, Ph.D.

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Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Comment
Sterility	Process parameters, container, formulation	4 (-2) = 2	5	5	50	(b) (4)
Endotoxin, pyrogen	Process parameters, container, formulation	2	4	4	32	
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	3	2	1	6	
Fill Volume/ deliverable volume	Formulation, process parameters, container closure	2	2	2	8	
Osmolality	Formulation, raw materials	2	3	2	12	
pH (High)	Formulation, raw materials, process parameters, container closure	3	4	1	12	
pH (High)	Formulation, raw materials, process parameters, container closure	2	2	1	4	
Particulate matter	Formulation, raw materials, process parameters, container closure	3	5	3	27	

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Comment
Leachable extractables	Formulation, raw materials, process parameters, container closure	2	4	3	24	
Appearance	Formulation, raw materials, process parameters, container closure	3	3	1	9	

Martha R. Heimann, Ph.D.

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Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN	Comment
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	3	2	3	18	(b) (4)
Dosing accuracy	Formulation, process parameters, container closure, dosing device	2	3	5	30	
Palatability	Formulation, excipient	3	3	5	45	
Microbial limits	Formulation, raw materials, process parameters	1	1	1	12	
Leachables	Formulation,, container closure	3	2	5	30	

Martha R. Heimann, Ph.D.

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