CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207145Orig1s000

CHEMISTRY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approve

NDA 207145
Review # 2

Drug Name/Dosage Form	Xadago (Safinamide) Tablets
Strength	50 mg, 100mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Newron Pharmaceuticals
US agent, if applicable	N/A

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD#: 0074 (resubmission)	9/21/2016	Drug Substance, Drug Product
SD#: 0079	12/20/2016	Labeling
SD#: 0080	1/27/2017	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Sharon Kelly	ONDP/DNDP I/Branch I
Drug Product	Martha Heimann	ONDP/DNDP I/Branch I
Process	N/A	OPF/DPA/Branch I
Microbiology	N/A	OPF/DMA/Branch I
Facility	N/A	OPF/DIA/Branch I
Biopharmaceutics	N/A	ONDP/DB/Branch I
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP I/Branch I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

Refer to Overall Quality Assessment, Review No. 1, dated February 10, 2016.

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

IND (b) (4) development of safinamide for treatment of Parkinson's disease.

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 207145 for Xadago® (safinamide) tablets

From a quality perspective, the application continues to provide adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Safinamide mesylate is a new chemical entity developed by the applicant, Newron Pharmaceuticals (Newron), as adjunctive therapy for patients with idiopathic Parkinson's disease (PD). The applicant proposes use of safinamide as an add-on to a single dopamine agonist monotherapy in early stage (b) (4) PD patients, and as an add-on to (b) (4) levodopa, alone or in combination with other PD medications, in mid- to late-stage PD patients. Safinamide is reported to act by multiple mechanisms, including state and use-dependent blockage of voltage-gated sodium channels, glutamate release inhibition, and reversible and selective Monoamino Oxidase B (MAO-B) inhibition.

Proposed Indication(s) including Intended Patient Population	Adjunctive treatment of patients with Parkinson's disease
Duration of Treatment	Chronic
Maximum Daily Dose	100 mg
Alternative Methods of Administration	None proposed

B. Quality Assessment Overview

The OPQ review team found NDA 207145 acceptable from a quality perspective, and recommended approval of the application, during the first review cycle. In the resubmission, the applicant proposes minor CMC revisions and updates.

Drug Substance

The applicant does not propose any changes to manufacture of the bulk drug substance or the drug substance specification limits. However, the drug product manufacturer,

(b) (4) has updated the acceptance testing monograph for safinamide. The updated monograph includes revisions to some analytical ranges (b) (4) with supporting validation data. The updated monograph also includes corrections to assay calculations and relative response factors for impurities. The applicant has incorporated batch analysis data from recent batches and provided updated stability reports.

Drug Product

The applicant added secondary containers (cardboard cartons) for the 30-count and 90-count HDPE bottles. This change does not impact on product quality. Based on evaluation of recent stability data versus the current product specifications, the proposed 36 month expiration dating period for tablets stored at controlled room temperature is acceptable.

Facilities

All facilities that will be involved in commercial manufacture and testing of Safinamide and Xadago® (safinamide) tablets are currently acceptable.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment for Safinamide Tablets

See Attachment 1.

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Recommendation: Approval

NDA 207145

Review # 1

February 10, 2016

Drug Name/Dosage Form	Safinamide Oral Tablets
Strength	50 mg and 100 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Newron Pharmaceuticals SpA
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	ONDP/DNDAPI/NDBI
Drug Product	Sherita McLamore	ONDP/DNDPI/NDPBI
Process	Mark Johnson	OPF/DPAI/PABI
Microbiology	Mark Johnson	
Facility	Tracie Sharp replaced with Franck Wackes	OPF/DIA/IABII
Biopharmaceutics	Okpo Eradiri	ONDP/DB/BBI
Project/Business Process Manager	Dahlia A. Woody	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Martha R. Heimann	ONDP/DNDPI/NDPBI
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	James Laurenson	ONDP/EA Team

QUALITY ASSESSMENT

NDA 207145

SUBMISSION(S) REVIEWED	DOCUMENT DATE
New NDA	05/27/2014
Quality Amendment	11/11/2014
Quality Amendment	01/15/2015
Quality Amendment	03/29/2015
Quality Amendment	05/12/2015
Quality Amendment	06/26/2015
Quality Amendment	08/27/2015
Quality Amendment	08/28/2015
Quality Amendment	09/09/2015
Quality Amendment	11/20/2015
Quality Amendment	12/01/2015
Quality Amendment	01/15/2015
Quality Amendment	01/26/2016

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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)	III	(b) (4)	(b) (4)	N/A	--	--
	III			N/A	--	--
	III			N//A	--	--
	II			Adequate	Sept. 02, 2015	Reviewed by Sharon Kelly, Ph.D.

[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	(b) (4)	Development of safinamide for treatment of Parkinson's disease

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

From a product quality perspective, NDA 207145 is recommended for approval. The applicant has satisfactorily addressed all deficiencies identified during the review process. As the review team concurs with the expiration dating period proposed by the applicant, there are no comments to be conveyed in the action letter.

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

Not Applicable

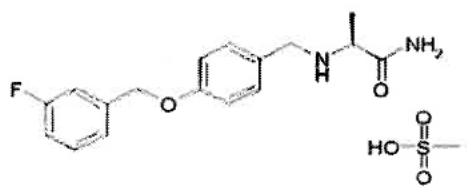
II. Summary of Quality Assessments

A. Drug Substance Quality Summary for Safinamide

Safinamide mesylate is a new chemical entity developed by the applicant, Newron Pharmaceuticals (Newron), as adjunctive therapy for patients with idiopathic Parkinson's disease (PD). The applicant proposes use of safinamide as an add-on to a single dopamine agonist monotherapy in early stage (b) (4) PD patients, and as an add-on to (b) (4) levodopa, alone or in combination with other PD medications, in mid- to late-stage PD patients. Safinamide is reported to act by multiple mechanisms, including state and use-dependent blockage of voltage-gated sodium channels, glutamate release inhibition, and reversible and selective Monoamino Oxidase B (MAO-B) inhibition.

Safinamide [chemical name: (*S*)-2-(((4-((3-fluorophenyl)methoxy)phenyl)methyl)-amino)propanamide methanesulfonate (1:1)] is a well characterized small molecule with molecular formula $C_{17}H_{19}FN_2O_2 \cdot CH_4O_3S$ and molecular weight 398.45 (302.34 as free base). There is one chiral center, (b) (4) (b) (4)

Chemical Structure of Safinamide



Safinamide mesylate is manufactured for the applicant by [redacted] The applicant provided drug substance information in the NDA as well as cross-reference to [redacted] The review team relied on the drug substance information provided in the NDA for evaluation with the exception of the process parameters and analytical procedures used by [redacted] for release testing. DMF [redacted] was reviewed and found acceptable to support approval of the NDA.

Safinamide mesylate is freely soluble in water [redacted]

[redacted]

The applicant's drug substance acceptance specification, as amended in response to information requests, includes appropriate tests to allow verification of all test parameters reported on the [redacted] certificate of analysis. The analytical procedures are straightforward and typical for a small organic molecule. The applicant indicates that the drug product manufacturer, [redacted] will routinely test for all parameters except quantitative content of the [redacted] which will be taken from the supplier's certificate of analysis (CoA). As the application includes an appropriate [redacted] procedure for use in periodic vendor qualification, acceptance based on the supplier's CoA is acceptable.

(b) (4)

(b) (4) Based on the stability data provided, a retest period of (b) (4) months is acceptable when stored at (b) (4).

B. Drug Product Quality Summary for Safinamide Tablets

The proposed products are immediate-release, film coated tablets containing 50 mg or 100 mg of safinamide as the mesylate salt. Both strengths are round, biconcave film-coated tablets which differ in diameter (7 mm and 9 mm for the 50 and 100 mg tablets, respectively) and debossing ("50" and "100") corresponding to tablet strength. The film-coat color, which is the same for both strengths is described as orange to copper, with a metallic gloss.

The 50 mg and 100 mg Safinamide tablet formulations are quantitatively proportional. The tablet cores contain safinamide mesylate and compendial excipients, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide. (b) (4) (b) (4) hypromellose, polyethylene glycol 6000, (b) (4) (titanium dioxide, potassium aluminum silicate, and iron oxide).

Safinamide tablets are manufactured by (b) (4)

(b) (4)

The specifications for 50 and 100 mg safinamide tablets include appropriate tests for an immediate release product, including description, identification by IR and HPLC, assay, dissolution, related substances impurities, content uniformity, water and microbial limits. All analytical procedures are adequately described and validated. The only significant impurity detected in the product is (b) (4) (b) (4)

Safinamide tablets are packaged in standard 30 mL (30-count) and 50 mL (90-count) HDPE bottles (b) (4) for commercial distribution. Physician samples will be packaged in (b) (4) blisters with aluminum foil backing. The container closure systems were chosen based on protection, safety and

compatibility with the drug product. Up to (b) (4) months of data were included for the drug products stored in the commercial container closure systems. The applicant proposed a (b) (4) month expiration dating period for the product when stored at room temperature. The proposed expiry is granted.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xadago is proposed
Non Proprietary Name of the Drug Product	Safinamide Tablets
Non Proprietary Name of the Drug Substance	Safinamide Mesylate
Proposed Indication(s) including Intended Patient Population	Adjunctive therapy in Parkinson's disease patients
Duration of Treatment	Chronic
Maximum Daily Dose	100 mg
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Designation: Safinamide exhibits low solubility and high permeability; it is therefore likely to be a BCS-2 compound.
   - Drug Substance: Highly soluble at pH 1.2 and 4.5 but shows low solubility at higher pH values (e.g., pH 6.8 and 7.5).
   - Drug Product: Safinamide Tablets are film-coated. The characteristics of the tablet formulation for BCS designation are no longer applicable since the drug substance physicochemical properties dictate a BCS-2 designation.

2. Biowaivers/Biostudies
   - Biowaiver Requests: The Applicant submitted two (2) biowaiver requests within the NDA. Firstly, a biowaiver request was made for the 50 and 100 mg strengths of the final formulation ((b) (4) Tablets). Since the change in formulation only affected the color of the film coat and the dissolution profile was unaffected, the biowaiver request is granted. The second biowaiver request was for bridging of the (b) (4) (b) (4) tablets to the capsules. Since the MOTION study alone was found by the clinical team to be sufficient to support the indication, the need to bridge the tablet to the capsule formulation was deemed no longer necessary.
   - PK studies: The Division of Biopharmaceutics reviewed the bioequivalence study (EMR 701165_021) conducted to bridge the (b) (4) (b) (4) Tablets to (b) (4) All other in-vivo PK studies were reviewed by the Office of Clinical Pharmacology.
   - IVIVC: None.

E. Novel Approaches

The applicant did not employ any novel approaches in the development or manufacture of safinamide tablets.

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)

I. Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The claim was reviewed and found to be acceptable.

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: 2016.02.10 19:18:24 -05'00'

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ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Safinamide is intended to be commercialized as 50 and 100 mg film-coated, immediate-release tablets for oral administration in the management of Parkinson's disease. The Biopharmaceutics review is focused on:

- Assessment of the dissolution method and acceptance criterion;
- Adequacy of bridging of the tablets manufactured [redacted] (b) (4)

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

The Applicant developed and validated a dissolution method intended for quality control of Safinamide Tablets at batch release and stability testing (table 1).

Table 1: Summary of dissolution method for Safinamide Tablets, 50 & 100 mg.

Instrument	Sotax AT7 smart equipped with UV spectrometer (AE031 and AE032)
Dissolution type	type 2 (paddle)
Dissolution medium	aqueous 0.1N HCl containing 20g/L sodium chloride, pH 1.2
Volume	900 mL
Temperature	37 ± 0.5°C
Rotation speed	100 rpm
Sampling method	on-line test
Wavelength of detection	227nm
Path length of cuvette	
Safinamide 50mg tablet	5 mm
Safinamide 100mg tablet	2 mm
Pulling time	after 5, 10, 15, 30, 45 and 60minutes dissolution

The proposed dissolution acceptance criterion is Q = [redacted] (b) (4) % at [redacted] (b) (4) min

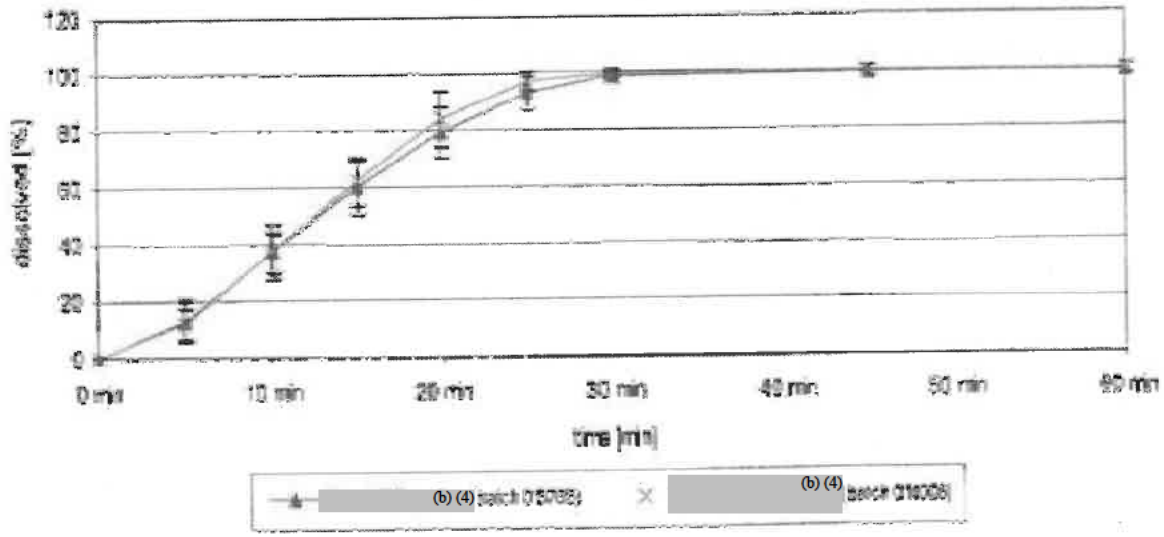
The following Question Based Review (QbR) approach was used to assess the proposed dissolution method.

39.1 Is dissolution/release acceptance criterion part of the regulatory specifications for release/stability? If yes, is full method development/validation report of the dissolution/release method included in the submission?

Yes, the Applicant submitted a dissolution method development report. The USP Apparatus 2 was chosen since it is mainly used for testing of tablet and capsule formulations. The Applicant compared the dissolution performance of Safinamide Tablets in SGFsp*, pH 4.5

buffer, pH 6.8 buffer, FaSSIF, and FeSSIF; SGFsp* (pH 1.2) was chosen as the dissolution medium. The paddle speed of 100 rpm was selected because some degree of coning was observed at 50 and 75 rpm. The dissolution profiles of the TBM product (b) (4) Tablets) and (b) (4) using the proposed dissolution method is displayed in figure 1.

Figure 1: Dissolution profiles of 100 mg Safinamide film-coated tablets [USP 2, 900 mL SGFsp*, 100 rpm].



The analytical method for the quantitation of safinamide in dissolution samples was validated for accuracy, linearity, specificity, precision, sample stability, and robustness parameters. All validation acceptance criteria were met and the method validation results are acceptable.

Information Request:

Regarding the dissolution acceptance criterion, the Applicant has not presented the supporting data in the NDA. A specification time point of (b) (4) min is proposed but no data at that time point was included in the initial NDA submission. The following IR was communicated to the Applicant on August 19, 2015:

> The dissolution acceptance criterion proposed in the Specifications table for the 50 and 100 mg strengths of Safinamide (b) (4) film-coated Tablets are not adequately justified by data. Although the proposed specification sampling time point is (b) (4) min, the data submitted in the stability and batch analysis sections contain data at only 45 min. Submit in tabular and graphical formats, the complete profile dissolution data (5, 10, 15, 30, & 45 min) for all clinical batches at release; at a minimum, submit dissolution data at 20, 25, 30 and 45 min. In a separate table, present a similar data set for all the registration batches at the zero (0) stability time point and over the 48-month stability period (long-term storage condition only). In addition to composite plots of the respective data sets at release (or at zero stability time point) and over 48 months, provide the overall mean percent safinamide dissolved at each time point and the associated overall range across all

clinical and registration batches. Please use the following tabular format to provide the dissolution data:

Batch Number	% Safinamide Dissolved Mean(n), [range], %CV				
	5 min	10 min	15 min	30 min	45 min
Grand Mean					
Overall Range					

Applicant's IR Response (received 8/27/2015):

The Applicant submitted responses to the IR comments on August 27, 2015. Dissolution data of clinical batches (50 and 100 mg strengths) at release were submitted at 15, 30, and 45 min (Fig 2).

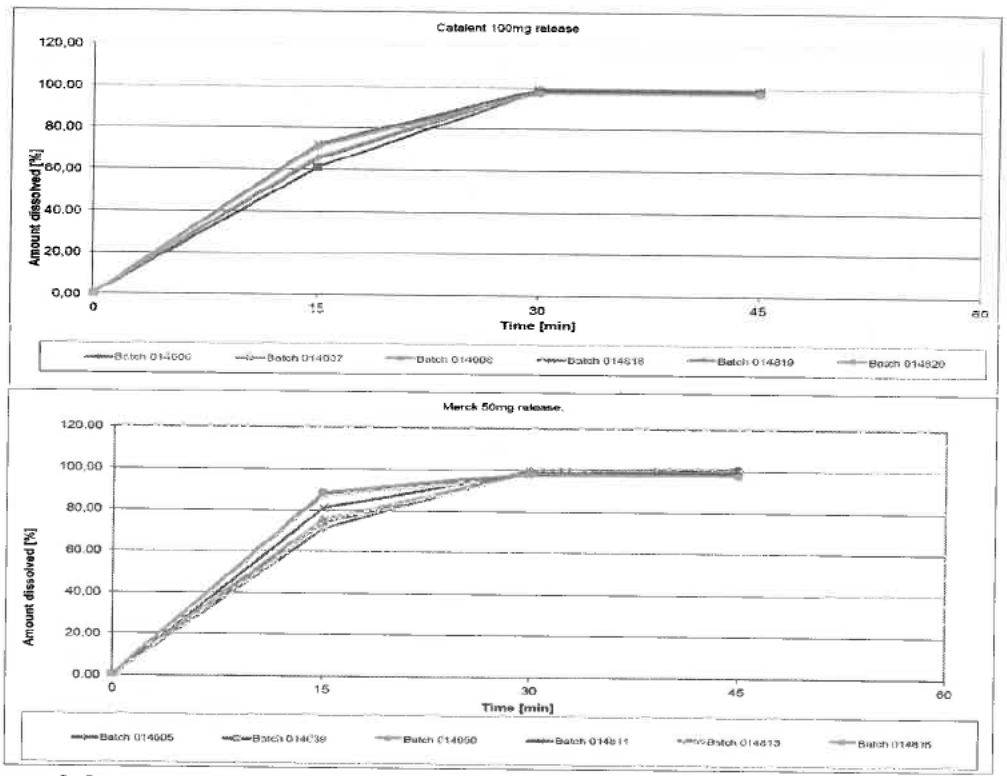


Figure 2: Mean safinamide dissolution profiles at release for 6 clinical batches each for the 100 mg (upper plot) and 50 mg (lower plot) strengths of Safinamide Tablets.

More detailed dissolution profile data for the registration batches at release (5, 10, 15, 20, 25, 30, 45 and 60 min) were submitted; the data for 9 batches of the 100 mg strength is presented in table 2. Similar results were observed for 9 batches of the 50 mg strength.

Table 2: Mean safinamide dissolution data at release for 9 registration batches for the 100 mg strengths of Safinamide Tablets.

Catalent	% Safinamide Released								
Batch No.	0	5	10	15	20	25	30	45	60
Batch 7401822									(b) (4)
Batch 7401823									
Batch 7411623									
Batch 7401825									
Batch 7401826									
Batch 7401827									
Batch 7401813									
Batch 7401814									
Batch 7401819									
Grand Mean [%]	0,00	23,12	50,55	74,27	90,94	98,01	99,02	99,23	99,28
min [%]		13,26	40,46	63,35	81,69	91,97	94,69	94,92	94,94
Max [%]		30,19	58,61	84,77	96,57	101,54	101,56	101,74	101,77
CV%		22,81	12,05	8,97	5,12	3,10	2,18	2,13	2,13

Although the clinical batches do not have data at the 20 and 25 min time points, it is evident that dissolution data at 15 and 30 min are similar for both clinical and registration batches. Based on the data in Table 2 and the submitted dissolution data for all stability batches in all packaging configurations, a specification time point of 20 min is appropriate for the drug product. The following comment is being conveyed to the Applicant to be discussed on Friday September 4, 2015:

> The FDA acknowledges receipt of your response (to the Biopharmaceutics IR) on August 27, 2015. Upon review of the newly submitted dissolution data for the clinical and registration batches in the different packaging configurations, FDA recommends a dissolution specification time point of 20 minutes. Amend the dissolution acceptance criterion of the proposed Safinamide Tablets to "**Q = (b) (4) % in 20 min**" and submit an updated Specifications table to the NDA. Please confirm your acceptance of this recommendation by email no later than close of business today, September 3, 2015; otherwise, schedule a teleconference for Friday September 4, 2015 to discuss and finalize the dissolution acceptance criterion.

Reviewer's Comments on Dissolution Acceptance Criterion:
The Applicant accepted the FDA's recommended dissolution acceptance criterion (Q = (b) (4) % in 20 min) on Friday September 4, 2015. The updated Specification tables for the 50 and 100 mg strengths of Safinamide Tablets were sent to the RBPM via email and they will be formerly submitted as an amendments to the NDA via the electronic gateway.

39.2 What data are available to support the discriminating power of the method?

The Applicant investigated the discriminating power of the dissolution method by conducting experiments on the following critical quality attributes:

- Particle size distribution (PSD)of the API
- Polymorphs (b) (4)
- Proportion of excipients (b) (4)
- Manufacturing parameters (b) (4)
  (b) (4)
- Film coating

Variant formulations (from the target) were made at laboratory scale and used in the experiments.

The results of the investigation of discriminating power of the proposed dissolution method are as follows:

(b) (4)

Reviewer's Comments: *The dissolution method demonstrated discriminating ability only when* (b) (4) (b) (4) *No other CQA affected the dissolution characteristics of safinamide tablets. The dissolution method cannot therefore be regarded as discriminating for formulation and manufacturing variables.*

39.3 Is the proposed dissolution/release method biorelevant? What data are available to support this claim?

Although simulated gastric fluid (SGFsp*) is used as the dissolution medium, there are no data in the submission that indicate the method is biorelevant.

39.4 Is there a NDA (e.g. 505(b)(1), 505(b)(2)) biowaiver request? What data (e.g., dose-linearity, compositional proportionality etc.) are available to support this request?

Yes, there were two biowaiver requests.

i. **Safinamide (b) (4) Tablets, 50 & 100 mg**: The 50 and 100 mg strengths of the intended commercial product were used in a number of clinical studies, including the absolute BA study (# EMR701165-022), a DDI study (#EMR701165-026), a safety renal impairment study (#EMR701165-027) and an open label dose escalation study (28849). It is therefore unclear why the Applicant submitted this biowaiver request.
ii. **Bridging of (b) (4) Tablets to Safinamide Capsules**: The clinical trial that was conducted with the capsule formulation was withdrawn from the NDA and only the MOTION trial carried out with the tablet formulation has been assessed by the clinical team. The bridging of the tablet and capsule formulations was therefore deemed unnecessary.

Reviewer's Comments: *The two biowaiver requests submitted in the NDA were no longer relevant at the time of review.*

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

Formulation changes were made during the development of the proposed drug product. A capsule formulation was initially used in clinical development (Trials 015 and 017). Thereafter, a (b) (4) tablet was developed (b) (4) (b) (4) and the tablets were used in the following 3 clinical studies: SETTLE, MOTION and Trial 018. According to the Applicant, (b) (4) (b) (4) the manufacturing of tablets resulting in a new tablet named (b) (4) Tablets". (b) (4) (b) (4) which is the intended commercial product. Both the (b) (4) tablets were used in various clinical studies.

The three tablet formulations (b) (4) were similar in their quantitative compositions and have been bridged through comparative dissolution testing. The (b) (4) tablets (b) (4) were bridged in a bioequivalence study (EMR 701165_021) using the 100 mg strength of both treatments. Since the MOTION study alone was found by the clinical team to be sufficient to support the indication, the need to bridge the capsule to the tablet formulations was deemed no longer necessary. The bioequivalence study (EMR 701165_021) conducted to bridge the (b) (4) Tablets to the (b) (4) has been reviewed and is summarized below.

STUDY NO. EMR 701165_021 : BIOEQUIVALENCE STUDY BRIDGING THE COMMERCIAL FORMULATION (b) (4) TABLETS) TO THE CLINICAL PHASE III FORMULATION (b) (4) TABLETS).

Study Title: A randomized, open-label, two-period crossover bioequivalence trial of two different oral tablets of 100 mg safinamide, utilizing different manufacturing processes, in healthy volunteers.

Objectives:

- Evaluation of bioequivalence of safinamide tablets (b) (4) (b) (4)
- Comparative safety of the two treatments in healthy volunteers (refer to the Clinical Safety review).

Design and Study Conduct:

Open-label, fasting, single-dose, randomized, single-center, 2-period, 2-treatment, 2-sequence, crossover.
n = 30 healthy subjects (15 M & 15 F), aged 24 – 55 y; n = 28 PK evaluable
Dropouts: 2 after Period 1
Washout = 17 days
2 Treatments administered orally under overnight fasting (≥ 10h) conditions:

- 1x100mg Safinamide Tablets, (b) (4) TBM, batch # 013785 – Test
- 1x100mg Safinamide Tablet, (b) (4) Clinical Phase III; batch # 0010610 - Reference

Blood sampling times – 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 h.
Anticoagulant – Lithium heparin
Long-term stability of safinamide in plasma – 22 months at -20 ˚C

The clinical portion of the study was initiated on 7/8/2009 and ended on 8/26/2009.

Analytes, Pharmacokinetics Parameters and Statistics:

The plasma samples were assayed for safinamide only in 10 analytical runs from 8/25/2009 to 9/22/2009. An LC-MS/MS method (# DMPK 76-09) was used to analyze plasma samples for lamivudine using an internal standard referred to as (b) (4) (lot ALC762-01-01); the molecular structure of the IS is (b) (4) g/mol whereas that for safinamide is (b) (4) g/mol. The calibration range of the method was 5 – 1000 ng/mL. The bioanalytical method was adequately validated and the incurred sample re-analyses results met the acceptance criteria.

The following PK parameters were calculated using non-compartmental methods with the software SAS, version 8.2: C_{max}, AUC0-t, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, λz, Vz/F, CL/F. ANOVA was used to compare log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ followed by construction of 90% confidence intervals around the respective geometric mean ratios for safinamide.

Results:

Twenty-eight subjects completed both Periods of the study; Subjects 19 and 28 dropped out for personal reasons and an acute intercurrent illness, respectively. The mean plasma safinamide concentration-time curves (n = 28) for both treatments are displayed in figure 1 while the mean PK parameters are presented in table 1.

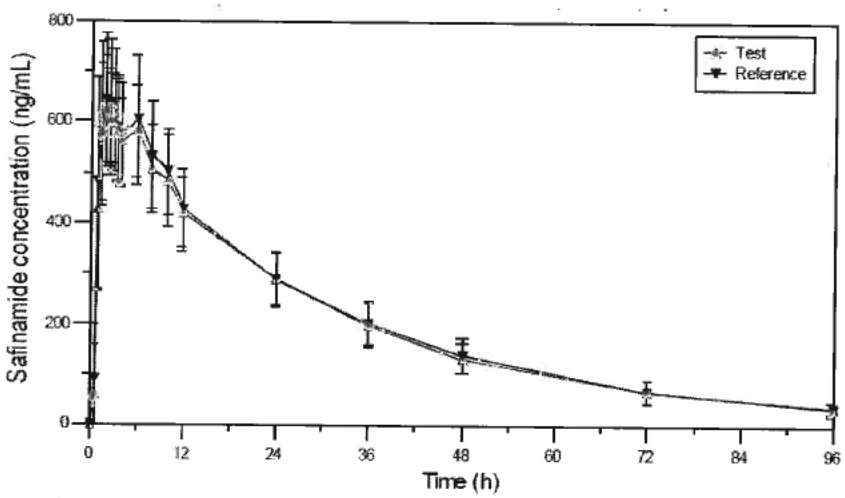


Figure 1: Safinamide mean plasma concentration-time profiles for (b) (4) Tablets (Test) and (b) (4) Tablets (Reference) after 100 mg single-dose administration to 28 healthy volunteers.

Table 1: Geometric mean plasma safinamide pharmacokinetic parameters [expressed as mean (%CV)] in healthy subjects; n = 29.

Parameter	T (Test Treatment) (b) (4)	R (Reference Treatment) (b) (4)
C_{max} (ng/mL)	646 (17.8) 396 – 889	685 (19.3) 461 – 1080
t_{max} * (h)	2.0 1.5 – 6.0	2.0 1.0 – 6.0
AUC_{0-t} (ng/mL*h)	18113 (20.1) 9785 – 24263	18583 (19.6) 10801 – 28661
$AUC_{0-\infty}$ (ng/mL*h)	19245 (21.3) 10177 – 27574	19715 (20.7) 11305 – 30035
$t_{1/2}$ (h)	23.4 (14.1) 19.2 – 32.0	23.1 (15.2) 16.9 – 34.8
CL/f (L/h)	5.20 (21.3) 3.63 – 9.83	5.07 (20.7) 3.33 – 8.85
V_z/f (L)	175.7 (18.6) 129.3 – 290.0	169.2 (21.9) 101.4 – 271.5

* median and range

The geometric 90% confidence intervals for the least squares mean safinamide AUC's and C_{max} are presented in table 2.

Table 2: Point estimates and 90% geometric confidence intervals for safinamide pharmacokinetic parameters.

Statistic	Treatment	PK Parameter		
		AUC_{0-t}, ng*h/mL	$AUC_{0-\infty}$, ng*h/mL	C_{max}, ng/mL
Least Squares Geom Mean	Test (b) (4) (b) (4)	18385	19527	656.0
	Ref (b) (4) (b) (4)	18353	19450	684.5
Point Estimate, % (90% CI)	Test/Ref	100.17 (98.25-102.1)	100.40 (98.39-102.4)	95.84 (92.77-99.01)

Based on the study results, the Applicant concluded that the final formulation (b) (4) (b) (4) is bioequivalent to the clinical batch manufactured (b) (4)

Reviewer's assessment of BE study: ***SATISFACTORY***

The Applicant's BE study results met all the acceptance criteria. The conduct of the study, assay validation and analytical runs as well as computations of PK parameters and their statistical analyses were reviewed. The geometric 90% confidence intervals for all three dose-dependent pharmacokinetic parameters were within 80 – 125% CI. The BE study results are therefore acceptable.

Reviewer's Overall Assessment:

1. The Applicant's proposed dissolution method is acceptable.
2. The final To-be-Marketed formulation of safinamide tablets (b) (4) was adequately bridged to the clinical batch through demonstration of bioequivalence in an in-vivo pharmacokinetic study.
3. The two biowaiver requests in the submission were deemed irrelevant at the point of review of the NDA.
4. The Applicant's proposed dissolution acceptance criterion (b) (4) was permissive and therefore unacceptable. A dissolution specification of Q = (b) (4)% in 20 min was therefore recommended. The Applicant accepted the FDA's recommended dissolution acceptance criterion (Q = (b) (4)% in 20 min) on Friday September 4, 2015. The updated Specification tables for the 50 and 100 mg strengths of Safinamide Tablets were sent to the RBPM via email and they will be formerly submitted as an amendments to the NDA via the electronic gateway.

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	None	Low	N/A	Acceptable	None. The dissolution method not discriminating for CQA's.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics had assessed NDA 207145 for Safinamide Tablets, 50 & 100 mg, and recommend the Application for APPROVAL.

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 assessments and final recommendation for approval of NDA 207145.

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

Date: September 4, 2015

Note: additional reviewers can be added, as appropriate

41. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?
42. 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?
43. 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: No materials of animal or human origin are used in manufacture.

Reviewer's Assessment: N/A

44. 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: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Application Technical Lead Comment:

Questions 43 and 44 are not applicable for this application. Per current Office of Process and Facilities policy for solid oral dosage forms, the microbiology aspects of the application were reviewed by the Process Reviewer, Mark Johnson. Refer to his evaluation under ASSESSMENT OF THE PROCESS, Question 35.

Martha Heimann, 9/3/215

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

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

Applicant's Response: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). Specifically, the expected introduction concentration (EIC) of safinamide was expected to by lower than 1 ppb, which would allow for a categorical exclusion from conducting an EA. The claim was accompanied by an adequate statement of no extraordinary circumstances.

Reviewer's Assessment: This application is for a new molecular entity, and in light of the new draft FDA guidance, Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity, this claim for an exclusion from an EA was reviewed in some detail.

The applicant's nonclinical toxicity data, section 2.4 Nonclinical Overview, noted that "apart from minor adrenal gland changes, the nonclinical program has not identified any endocrine disruption potential which may pose a human risk." However, as noted in the Preclinical Reproductive and Developmental Risk Assessment for section 2.4, "the findings encountered in the comprehensive reproductive toxicity study programme suggest that Safinamide when given alone, or even more so when given in combination with dopaminergic co-medications, is predicted to increase the risk of adverse developmental and perhaps reproductive outcomes in humans when used in accordance with the dosing information in the product label." Furthermore, the lowest no observed adverse effects level (NOAEL) found in the nonclinical data was 12.5 mg/kg/day, which is lower than 45 mg/kg/day, which is a NOAEL cutoff we currently are testing for use for screening for effects in the aquatic environment for drugs with EICs at or around 1 ppb.

Examining the literature, an EA was found to be in progress through an EMA application (EMA, 2014, Assessment report, Xadago [safinamide]). Preliminary data was included:

(b) (4)

(b) (4)

[redacted]

This is a robust set of data, and thus the lowest no observed effects concentration (NOEC) of (b) (4) mg/L for algae would be a reasonable comparison to the EIC.

The EIC was not provided, but based on ~500K patients w/Parkinsons in the US (http://nihseniorhealth.gov/parkinsonsdisease/whatisparkinsonsdisease/01.html) and the maximum dose proposed of 100 mg/day, the maximum EIC is (b) (4) µg/L. The risk quotient thus is (b) (4) Because this is substantially less than 1, the categorical exclusion from an EA is appropriate.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL ANALYSIS

Reviewer's Assessment and Signature:

The applicant provided an appropriate claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The claim was reviewed and found to be acceptable.

Signed:
James P. Laurenson, MS, 2/3/2015
ONDP/Environmental Assessment Team

Supervisor Comments and Concurrence:

I concur with the above review.

Signed:
M. Scott Furness, Deputy Director, ONDP

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

Labeling & Package Insert

1. Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XADAGO safely and effectively. See full prescribing information for XADAGO.

XADAGO tablets, for oral use
Initial U.S. Approval: 2015

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Xadago	established name missing
Dosage form, route of administration	Tablets	adequate
Controlled drug substance symbol (if applicable)	n/a	n/a
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	The drug product is presented as 50 and 100 mg immediate release tablets.	adequate

Conclusion: Correction to product title will be made in the DNP working version of the PI.

(b) "Full Prescribing Information" Section

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

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

- 50 mg: orange to copper with metallic gloss, round, biconcave shaped embossed with "50" on one side
- 100 mg: orange to copper with metallic gloss, round, biconcave shaped embossed with "100" on one side

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Dosage form included	adequate
Strengths: in metric system	The reviewer notes that the strengths for each of the two tablets are listed in the metric system (50 and 100 mg)	adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Full description including color shape and embossing included (See information above)	adequate

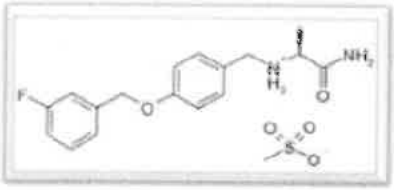
Conclusion: Information is adequate to support the approval of application

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

11 DESCRIPTION

XADAGO tablets contain safinamide (b) (4) (b) (4)

Safinamide mesylate is propanamide, 2-[[[4-[(3-fluorophenyl) methoxy]phenyl]methyl]amino]-, (2S), methanesulfonate (1:1) and its structural formula is below.

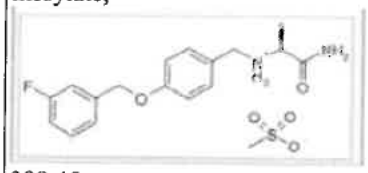


The molecular formula of safinamide mesylate is $C_{17}H_{19}FN_2O_2.CH_4O_3S$ and its molecular weight is 398.45.

Safinamide mesylate is a white to off-white crystalline powder. Safinamide mesylate is freely soluble in water, methanol and dimethyl sulphoxide. Safinamide mesylate is (b) (4) is practically insoluble in ethylacetate. In aqueous buffers that span a pH range of 1.2 to 7.5, safinamide mesylate is highly soluble at pH 1.2 and 4.5, but shows low solubility (< 0.4 mg/mL) at pH 6.8 and 7.5.

XADAGO (b) (4) available as 50 mg and 100 mg film-coated tablets. Each XADAGO tablet contains safinamide mesylate equivalent to 50 mg or 100 mg of safinamide free base. The tablets also contain the following inactive ingredients: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol 6000, iron oxide (red), potassium aluminum silicate, and titanium dioxide. (b) (4) (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Information included: XADAGO safinamide	adequate
Dosage form and route of administration	Information included: tablet	adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Information included: Each table contains safinamide mesylate equivalent to 50 mg or 100 mg of safinamide free base	n/a
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Information included: microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol 6000, iron oxide (red), potassium silicate, and titanium dioxide	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Information Included: Treatment of idiopathic Parkinson's disease.	adequate
Chemical name, structural formula,	Information included: Safinamide	adequate

molecular weight	mesylate,  398.45	
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa, solubility, or pH)	n/a	n/a

Conclusion: Information is adequate to support the approval of application

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 (b) (4)

50 mg (orange to copper colored with metallic gloss, round film-coated, biconcave shaped tablet embossed with "50" on one side; approx. 7 mm in diameter).

Bottles of 30 tablets.....NDC XXXXX-XXX-XX
Bottles of 90 tablets.....NDC XXXXX-XXX-XX
(b) (4)

100 mg (orange to copper colored with metallic gloss, round film-coated, biconcave shaped tablet embossed with "100" on one side; approx. 9 mm in diameter).

Bottles of 30 tablets.....NDC XXXXX-XXX-XX
Bottles of 90 tablets.....NDC XXXXX-XXX-XX
(b) (4)

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP controlled room temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Information included: 50 mg and 100 mg	adequate
Available units (e.g., bottles of 100 tablets)	Information included: bottles of 30 tablets; bottles of 90 tablets (b) (4) (b) (4)	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Information included: see above	adequate
Special handling (e.g., protect from light, do not freeze)	No special handling noted	adequate
Storage conditions	Information included: Standard USP controlled room temperature statement.	adequate

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

Distributed and Marketed by:
Newron Pharmaceuticals US, Inc.
{Address to be determined}
Marketed by:
{To be determined}

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Information included: Newron Pharmaceuticals US Inc.	adequate

Conclusion: Information is adequate to support the approval of application

2. Labels

(b) (4)

Conclusion: Adequate

2) Cartons

(b) (4)

Conclusion: Adequate

II. List of Deficiencies To Be Communicated

Not applicable

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			NME API	Acceptable based on manufacturing history
			None	Acceptable based on manufacturing history
			None	Acceptable based on manufacturing history
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)			None	Acceptable based on manufacturing history
			None	Acceptable based on manufacturing history
			None	Acceptable based on manufacturing history
			None	Acceptable based on manufacturing history

B. Lifecycle Knowledge Management

a) Drug Substance

A formal risk assessment for the drug substance was not performed. Based on an initial assessment of the application, the following risks were noted.

From Initial Assessment		Review Assessment		
Risk Factor	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
[redacted] (b) (4)			Acceptable Acceptable	Reassess if process changes.
			Acceptable	

Past interactions between the drug substance manufacturer, [redacted] (b) (4) and the applicant, include:

[redacted] (b) (4)

Based on this history, it is possible that Newron will transfer drug substance manufacture to a new contract facility as a post-approval change.

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	Excipient compatibility evaluated during formulation development. (b) (4)	Acceptable	
Content uniformity	Low dose, particle size/shape, segregation, flow property	L		Acceptable	
Physical (solid state) stability	Formulation, process parameters, moisture	M		Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	Very L	Control in product specification	Acceptable	
Dissolution	Particle size, moisture, hardness, size, shape, film coat, formulation, process parameters	M	Process understanding based on QbD approach. Additional risk assessment (b) (4)	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.