CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209229Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209229

Review #1

Drug Name/Dosage Form	Lucemyra (Lofexidine Hydrochloride) tablet
Strength	0.18 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	US Worldmeds LLC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Seq. 001	*5/13/2017*	
Seq. 002	*7/28/17*	
Seq. 005	*9/26/17*	
Seq. 011	*11/22/2017*	
Seq. 019	*1/24/18*	
Seq. 023	*2/16/18*	
Seq. 025	*3/28/18*	
Seq. 028	*4/13/2018*	
Seq. 029	*4/17/2018*	

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Debasis Ghosh	Donna Christner
Drug Product	Venkat Pavuluri	Julia Pinto
Process	Haitao Li	Ubrani Venkataram
Microbiology		
Facility	Wenzheng Zhang/Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Bryan Ericksen/Kelly Kitchens	Tapash Ghosh
Regulatory Business	Steven Kinsley	

Process Manager		
Application Technical Lead	Ciby Abraham	
Laboratory (OTR)		
ORA Lead	Caryn McNabb, Michael Tollen	
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	IV		(b) (4)	Adequate	4/17/2018	Information in NDA
	IV			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA
	III			Adequate	4/17/2018	Information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A - NME		

2. CONSULTS –N/A

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

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, drug product, process, microbiology, facilities, and biopharmaceutics, CMC recommends approval of Lucemyra (Lofexidine HCl) 0.18 mg tablets.

II. Summary of Quality Assessments

A. Product Overview

Lofexidine HCl immediate release tablets 0.18 mg is proposed to mitigate the symptoms associated with opioid withdrawal and to facilitate the completion of an opioid discontinuation program. The proposed dosing regimen is 3 tablets QID for a total daily dose of 2.16 mg, or 4 tablets QID for a total daily dose of 2.88 mg.

N/A	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	Lofexidine is a (b) (4) adrenergic (b) (4) agonist indicated for: • mitigation of symptoms associated with opioid withdrawal; • facilitation of completion of opioid discontinuation treatment.
Duration of Treatment	0.72 mg (4 x 0.18 mg tablets) 4 times daily (2.88 mg total daily dose) taken orally at 5- to 6-hour intervals for 7 days. (b) (4) (b) (4)
Maximum Daily Dose	2.88 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Lofexidine HCl is provided as a 0.18 mg round, peach-colored, film-coated tablet, imprinted with "LFX" on one side and "18" on the other side. The drug product is packaged in (b) (4) count white round 30 cc HDPE bottles with a (b) (4) screw cap closure. Each bottle contains (b) (4) desiccant packaged in a (b) (4) sachet. The manufacturing process for lofexidine 0.18 mg tablets consists of (b) (4), (b) (4) (b) (4) Lactose is used as a (b) (4) povidone as the (b) (4) and calcium stearate as a (b) (4) All excipients used in the production of lofexidine tablets comply with applicable USP/NF monograph standards.

Lofexidine HCl drug substance is a white to off-white crystalline solid with a melting point between 236°C to 238°C. There are two polymorphic forms of the drug substance, (b) (4) The drug substance polymorphism and particle size distribution are not critical attributes that will affect product performance since the tablets are manufactured using (b) (4) . The drug substance has a retest period of (b) (4) months at (b) (4) % RH.

The expiry of 36 months is granted for Lucemyra when stored at room temperature, (b) (4) 25°C (b) (4) excursions permitted to 15-30°C (59-86°F) in (b) (4)-count white round 30 cc HDPE bottles. Each bottle contains (b) (4) desiccant packaged in a (b) (4) sachet.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking ***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters •	L	-	N/A	-

	Scale/equipment • Site				
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	-	L	(b) (4)
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

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LABELING

IQA Review Guide Reference

{For NDA 209229}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Lucemyra™ is approved proprietary name, but was not included in the PI as of this review date (18-MAR-2018). Established Name: LOFEXIDINE tablet.
Dosage form, route of administration	Tablet, Oral
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablet, 0.18 mg

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not Applicable for this immediate release tablet for oral administration.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	0.18 mg
Active moiety expression of strength with equivalence statement (if applicable)	Lofexidine 0.18 mg (Though Lofexidine Hydrochloride was the form used, dose was expressed as Lofexidine)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Round, convex-shaped peach colored film-coated tablet imprinted with "LFX" on one side and "18" on the other.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Lucemyra™ is approved proprietary name, but was not included in the PI as of this review date (18-MAR-2018). Established name: Lofexidine tablet
Dosage form and route of administration	Tablet, Oral
Active moiety expression of strength with equivalence statement (if applicable)	Each tablet contains 0.2 mg of lofexidine hydrochloride, equivalent to 0.18 mg of lofexidine free base. Active moiety expressed as free base, i.e. Lofexidine 0.18 mg.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not applicable for the oral solid dosage form. However, sponsor included the quantities of all inactive ingredients used in the drug product.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	(b) (4) agonist, Used for mitigation of symptoms associated with opioid withdrawal.
Chemical name, structural formula, molecular weight	Adequate as included in the PI
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not provided

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	0.18 mg, Tablet
Available units (e.g., bottles of 100 tablets)	Bottle of (b) (4) tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Round, peach colored, film-coated tablets, imprinted with "LFX" on one side and "18" on the other side; approximately 7mm in diameter.
Special handling (e.g., protect from light)	No special handling required.
Storage conditions	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate information included.

Reviewer's Assessment of Package Insert: Inadequate.

Storage conditions under section 16 of the PI, to include "Keep away from heat and moisture" per the stability summary.
Approved Proprietary Name, Lucemyra™, may be included in the PI at the discretion of the sponsor.

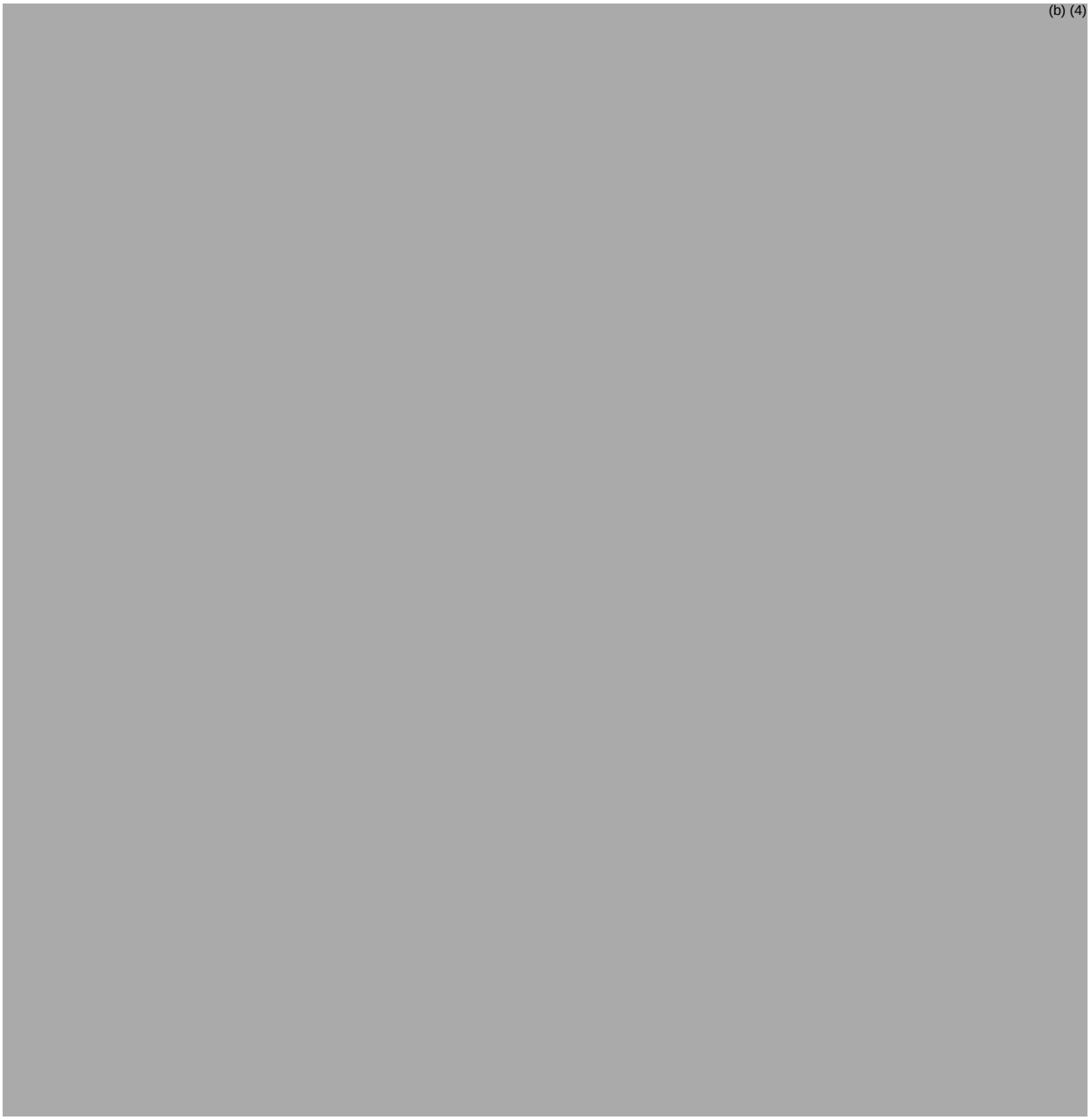
- Provide revised Prescribing Information, with inclusion of "Keep away from heat and moisture" (b) (4) next to the USP Controlled room Temperature.
- Prescribing Information may be revised to include approved Proprietary name, i.e. LUCEMYRA™.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

2. *Carton Label*



Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Meets the requirement for prominence of the established name	Meets the requirement for prominence of the established name
Dosage strength	Included, Added color block to strength and changed font color.	Included, Added color block to strength and changed font color.
Net contents	Included	Included
"Rx only" displayed prominently on the main panel	Included	Included
NDC number (21 CFR 207.35(b)(3)(i))	Included	Included
Lot number and expiration date (21 CFR 201.17)	Included, Expiration date format changed to yyyy/mm.	Included, Expiration date format changed to yyyy/mm.
Storage conditions	"Keep away from heat and moisture" was added next to the statement as per USP recommended storage conditions, per the stability summary.	"Keep away from heat and moisture" was added next to the statement as per USP recommended storage conditions, per the stability summary
Bar code (21CFR 201.25)	Included	Included
Name of manufacturer/distributor	Distributor name included	Distributor name included
And others, if space is available	None	None

Reviewer's Assessment of Labels: Inadequate.

- Revised container and carton labels with inclusion of "Keep away from heat and moisture", in addition to the USP controlled room temperature.

List of Deficiencies:

Prescribing Information may be revised to include the following:

1. Section 3 may be revised as: LUCEMYRA™ is available as round, peach-colored, film-coated tablet, imprinted with "LFX" on one side and "18" on the other side, contains Lofexidine 0.18 mg (equivalent to 0.2 mg of Lofexidine Hydrochloride).

2. Section (b) (4) to include the statement "Keep away from heat and moisture" was added next to the statement as per USP recommended storage conditions, per the stability summary.

3. Approved Proprietary name, i.e. LUCEMYRA™ may be inserted throughout the PI, as applicable.

Overall Assessment and Recommendation: **Approvable, subject to minor edits to the PI as recommended above.**

Primary Labeling Reviewer Name and Date: Venkateswara R. Pavuluri, Ph.D.; R. Ph.

18-APR-2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Julia C. Pinto, Ph. D.

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 4/18/2018 10:07:07AM
GUID: 551eb409003b6d46b8d5dfa7699e4742
Comments: Except for the changes required in PI, labeling is adequate.

Julia Pinto

Digitally signed by Julia Pinto
Date: 4/18/2018 11:18:56AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: March 12, 2018

To: Debasis Ghosh, Drug Substance Reviewer
Venkat Pavuluri, Drug Product Reviewer
Steven Kinsley, RBPM

Through: Jason Rodriguez, Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Cindy Ngo, Chemist, CDER/OPQ/OTR/DPA
Tim Andres Marzan, Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, Project Manager, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 209229:Lofexidine Hydrochloride Tablet 0.18 mg.

The following method was evaluated and is *acceptable with modification* for quality control and regulatory purposes:

1. Related Substances and Assay of [redacted] (b) (4) by HPLC from [redacted] (b) (4) [redacted] (b) (4)/222/7, page 1-5, Issue February 2017.

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the method:

1. [redacted] (b) (4)
2. The method did not list the reporting threshold or limit of quantitation (LOQ) for the specified impurities [redacted] (b) (4) and individual unspecified

impurity. DPA recommends the preparation of a Standard Solution at the quantitation limit or at the very least, the specification limit for [redacted]

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8819ee911

Summary of Analysis

Lofexidine Hydrochloride lot# 35003200:

Results	Sample	Average	Specifications
% Assay	Lodexidine HCl	100.1	[redacted]%, Pass
[redacted]			
% Impurity	[redacted]	[redacted]	NMT [redacted]%, Pass

Lofexidine Hydrochloride lot# 35003201:

Results	Sample	Average	Specifications
% Assay	Lodexidine HCl	101.3	[redacted]%, Pass
[redacted]			
% Impurity	[redacted]	[redacted]	NMT [redacted]%, Pass

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BIOPHARMACEUTICS

Product Background:
This Section 505(b)(1) submission is for a new chemical entity, lofexidine hydrochloride (HCl) tablets (0.18 mg), for the indications of "mitigation of symptoms associated with opioid withdrawal" and "facilitation of completion of opioid discontinuation treatment".

NDA: 209229

Drug Product Name / Strength: Lofexidine Hydrochloride Tablets / 0.18 mg

Route of Administration: Oral

Applicant Name: US WorldMeds, LLC

Review Recommendation: **Adequate**

Review Summary:

List Submissions being reviewed (table):

05/03/2017	Sequence 0001 Presubmission to Original NDA Rolling Submission
07/28/2017	Sequence 0002 Module 2.7.1 summary-biopharm-analyt-methods
09/26/2017	Sequence 0005 Module 3.2.P.2. Pharmaceutical Development
02/16/2018	Sequence 0023 Response to Information Request

Highlight Key Outstanding Issues from Last Cycle:

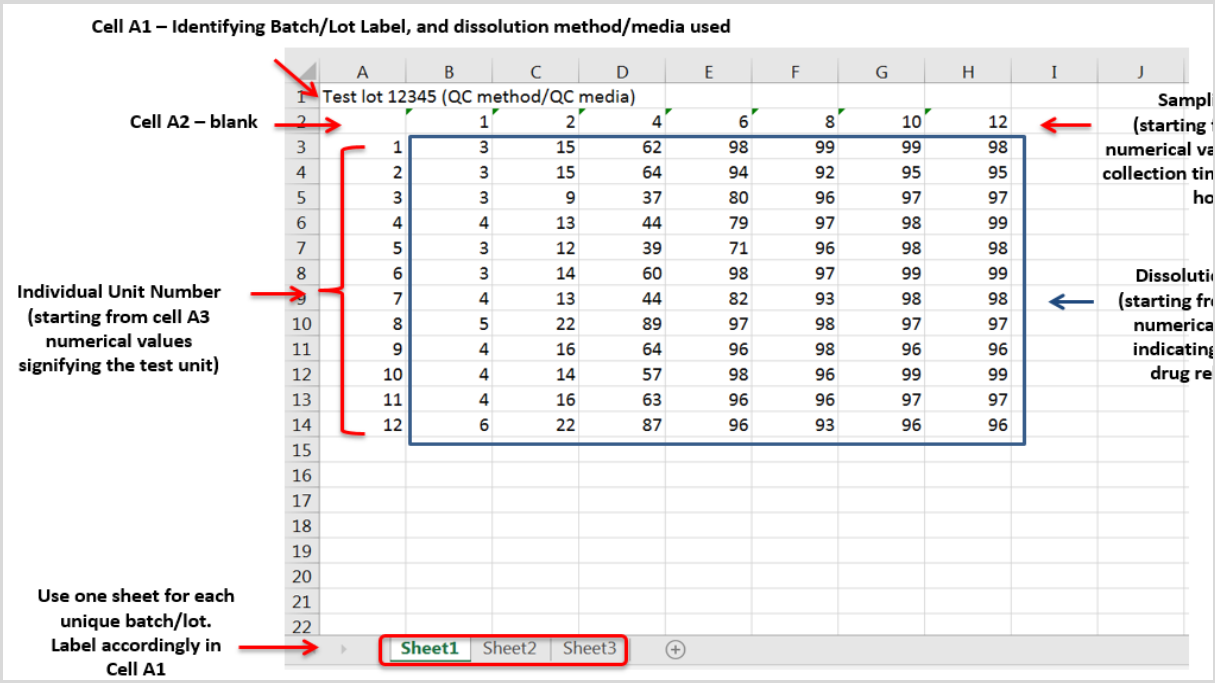
1. Submit the complete dissolution data [i.e. individual (n=12), mean, SD, % CV at each time point] for the dissolution profiles generated from the discriminatory power studies, i.e. the complete dissolution data from Figures 7-10 in your Dissolution Method Development Report.
2. Submit complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.
3. Submit complete dissolution data for all (b) (4) and Catalent batches used to justify your proposed dissolution acceptance criterion. We recommend that you revise the dissolution acceptance criterion to the sampling time point where Q = (b) (4) % dissolution occurs, based on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).

4. Provide an explanation for the high variability observed at the early dissolution time points.

Dissolution Data Presentation: In the dissolution method development report and/or batch analysis section, present detailed experimental dissolution data as follows:

- In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
- In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
- Provide in your NDA the dissolution data as described in the example below.

Example - Reporting of individual vessel dissolution data



	A	B	C	D	E	F	G	H
1	Test lot 12345 (QC method/QC media)							
2		1	2	4	6	8	10	12
3	1	3	15	62	98	99	99	98
4	2	3	15	64	94	92	95	95
5	3	3	9	37	80	96	97	97
6	4	4	13	44	79	97	98	99
7	5	3	12	39	71	96	98	98
8	6	3	14	60	98	97	99	99
9	7	4	13	44	82	93	98	98
10	8	5	22	89	97	98	97	97
11	9	4	16	64	96	98	96	96
12	10	4	14	57	98	96	99	99
13	11	4	16	63	96	96	97	97
14	12	6	22	87	96	93	96	96

Concise Description Outstanding Issues Remaining: There are no outstanding issues. However, the Applicant will be advised to explore the use of sinkers to reduce the variability in dissolution data. If the Applicant decides to use sinkers in the dissolution method, the Applicant will need to provide justification and dissolution data to support the selected sinker, and update the dissolution method with a detailed description of the selected sinker.

BCS Designation

Reviewer's Assessment: The Applicant did not make a BCS designation claim. The Applicant suggests that the assignment of BCS Class 1 for lofexidine HCl is justified based on the permeability and solubility data summarized below.

Solubility: Solubility information was submitted in module 3.2.S.1, General Information, as shown in the table below.

Table 1: General Properties

Property	Attribute			
Chemical name	2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1*H*-imidazoline monohydrochloride			
Appearance	White to off-white crystalline solid			
pH	5.1 (2% w/v solution)			
pKa (25°C)	9.43 (free base)			
Log *P* (Octanol/Water)	3.58			
Optical rotation	0° (racemic mixture)			
Polymorphism	Lofexidine HCl exists in two (b) (4) The drug substance produced by (b) (4)			
Solubility (25°C)	**Solvents**	**Solubility (mg/mL)**		**Compendial Description**
	Methanol	684		Freely soluble
	Ethanol	320		Freely soluble
	Chloroform	9.7		Slightly soluble
	n-Hexane	0.24		Very slightly soluble
	Benzene	0.22		Very slightly soluble
Aqueous solubility (24 hour equilibrium)	**Solution/Buffer**	**Theoretical pH**	**pH after 24 hrs.**	**Solubility (mg/mL)**
	0.1N HCl	1	1.13	382
	Acid Phthalate (USP)	3	2.55	440
	Acetate (USP)	4.5	4.38	421
	Water	n/a	5.08	421
	Phosphate (USP)	6	5.63	416
	0.1 M Phosphate	7.2	6.64	405
	Phosphate (USP)	7.6	6.68	396
	Borate (USP)	9	7.63	25.6
	Borate (USP)	10	8.14	7.75
Particle size	Monomodal distribution, observed particle size ranges: Mean: (b) (4) D_{10}: D_{50}: D_{90}:			
Melting point	236°C (onset) 238°C (peak) accompanied by decomposition and a negligible weight loss of 0.02% between 25°C and 150°C (Lot 28003072).			

A screening study of lofexidine HCl was carried out using numerous (b) (4) Only two polymorphs, designated (b) (4) were identified. Solubility information was submitted in module 3.2.S.3., section 1.3.2.2. The solubility of lofexidine HCl was assessed in 5 organic solvents and a series of aqueous buffers and in water. Solubility

(b) (4)

Based on the results of the solubility study, lofexidine HCl can be described as "freely soluble," per USP 34 over the pH range of (b) (4), in which the range of solubility is (b) (4) mg/mL. (b) (4)

(b) (4)

Permeability: Data to support the high permeability of the drug product was generated in a radiolabeled pharmacokinetic study (USWM-LX1-1003-1) that showed that nearly all of the lofexidine dose was absorbed, and that the primary route of elimination of the parent drug and its metabolites is via the kidney. The high extent of recovery indicates that lofexidine can be classified as a high permeability drug in that greater than 90% of the administered dose was absorbed.

Dissolution: Because of the extreme aqueous solubility of the drug substance, and the small active content per tablet (0.2 mg lofexidine HCl), there are no typical dissolution method conditions in which the active API dissolved in the medium would not be far in

(b) (4)

Thus, the drug substance concentration in the dissolution method is a factor of 10^6 below the solubility limit, as shown in the following table.

Table 2: Dissolution Method Drug Substance Concentrations

Dissolution Parameter	Value
Lofexidine HCl per tablet	0.2 mg
Dissolution volume	500 mL
Concentration in dissolution medium	0.0004 mg/mL
Solubility of lofexidine HCl at neutral pH	~400 mg/mL

Dissolution Method and Acceptance Criterion

Reviewer's Assessment: ***Adequate***
In the 02/16/18 Response to the 01/26/2018 Information Request (IR), the applicant submitted complete dissolution profiles for a (b) (4) lot, stressed and unstressed, and five Catalent lots. Although the applicant reported f2 values in a comparison of commercial and development methods (see Table 3, below), and these f2 values cannot be confirmed by the reviewer, these f2 values are not needed for bridging of formulations. In addition, the applicant stated that all dissolution data were provided in this response to IR. Therefore, this response is adequate.

Acceptance Criterion

In module 3.2.P.5.6, Justification of Specifications, the applicant proposed the acceptance criterion of NLT (b) (4)% (Q) dissolved at 30 min. The Applicant was requested to submit complete dissolution data for the (b) (4) and Catalent batches in the January 26, 2018 IR letter. It appears that a revised specification of NLT (b) (4)% (Q) dissolved at 30 min is appropriate based on the data submitted. The Applicant also proposed a revised dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 minutes. This acceptance criterion is adequate based on the dissolution data submitted.

Dissolution Method

The applicant used the following dissolution method conditions (Table 1):

Table 1: Final dissolution method conditions

Parameter	Condition
Medium	0.025M Potassium phosphate buffer, pH 7.2
Volume	500 mL
Temperature	37°C ± 0.5°C
Speed of rotation	50 rpm
Apparatus	USP Apparatus 2 (paddles)
Evaluation time	30 minutes (Q = (b) (4)%)
Profile	5, 10, 15, 20, 30, and 45 min (if required)
Withdrawal volume	9 mL
Sample analysis	HPLC Method (b) (4)0370

Dissolution profile data collected on a single lot from (b) (4) and five lots manufactured by Catalent were used to select and justify the 30 minute evaluation time (Figure 1 and Table 2).

Figure 1: Average and Individual Low and High Dissolution Values

Note: Error bars represent the individual high and low dissolution values at each time point. Each time point represents a mean of the 6 lots (presented in Table 2).

Table 2: Summary of Profile Dissolution Results for (b) (4) and Catalent Tablets

Manuf.	Batch Number	Summary Dissolution Results (Minutes)						
		Parameter	5	10	15	20	30	45
(b) (4)	33405-5588 (n=12)	Avg. (% Release)	13	44	68	83	95	100
		RSD	31	18	13	12	6	3
		Range (% Release)	(b) (4)					

Manuf.	Batch Number	Summary Dissolution Results (Minutes)						
		Parameter	5	10	15	20	30	45
Catalent	1639797 (n=6)	Avg. (% Release)	20	49	71	87	93	96
		RSD	38	20	14	10	7	4
		Range (% Release)	(b) (4)					
	1645244 (n=6)	Avg. (% Release)	19	50	72	84	92	95
		RSD	54	29	23	16	8	3
		Range (% Release)	(b) (4)					
	1645697 (n=6)	Avg. (% Release)	24	50	70	83	91	96
		RSD	21	21	17	13	8	5
		Range (% Release)	(b) (4)					
	1649979 (n=12)	Avg. (% Release)	16	51	77	91	96	97
		RSD	61	22	14	8	4	3
		Range (% Release)	(b) (4)					
	1649981 (n=12)	Avg. (% Release)	21	52	77	91	97	98
		RSD	38	20	12	9	4	3
		Range (% Release)	(b) (4)					
Average (Range):								
Relative Standard Deviation (Range):								
Absolute Range for all Batches:								

See the method development section, below, for the history of (b) (4) and Catalent.

(b) (4)

(b) (4)

[redacted]

In their response to IR dated 01/26/2018, the applicant provided a discussion regarding the root cause of the high variability in dissolution results (> 20% RSD in the earliest time point and > 10% RSD thereafter). The small size of tablets was cited, and the applicant noted that tablets do not always sink to the bottom of the dissolution chamber immediately. This Applicant's response is satisfactory. However, the Applicant will be advised to explore the use of sinkers to reduce the variability in dissolution data. If the Applicant decides to use sinkers in the dissolution method, the Applicant will need to provide justification and dissolution data to support the selected sinker, and update the dissolution method with a detailed description of the selected sinker.

(b) (4)

[redacted]

(b) (4)

[redacted]

Comparison of Tablets Manufactured at Two Different Sites

The only changes to the drug product formulation were made early in development, and the same formulation, tablet strength (0.18 mg), and (b) (4) has been used to produce tablets for all clinical trials since approximately 1983. All development and clinical study batches of lofexidine tablets were manufactured at commercial scale (b) (4) yielded product of acceptable and reproducible quality. Then in preparation for NDA submission in 2015, a comprehensive

review of the manufacturing process was performed with the goal of identifying and investigating critical process parameters (CPP) and critical quality attributes (CQA) for in-process materials and the finished product. Three placebo batches and one active batch were manufactured and tested under protocol to increase process knowledge and justify process ranges using QbD principles. Note that the placebo formulation was considered representative of the active formulation (in terms of physical properties) because the formulation contains only (b) (4) of the drug substance.

(b) (4)

occurred for business reasons only and was not the result of any GMP-related or regulatory enforcement action. Commercial manufacturing of lofexidine tablets has since been transferred to Catalent Pharma Solutions (Winchester, KY) where 7 full scale lots have recently been manufactured and 2 GMP lots have been placed on stability. Batch analysis results of the Catalent tablets show they are comparable to (b) (4) tablets and equivalence of the product manufactured at both sites was shown with a comparison of the dissolution profiles.

A comparison of the dissolution profiles for tablets manufactured at both (b) (4) and Catalent demonstrates that the dissolution profiles are similar as determined using f2 comparison, as shown in Table 7 and Figure 10.

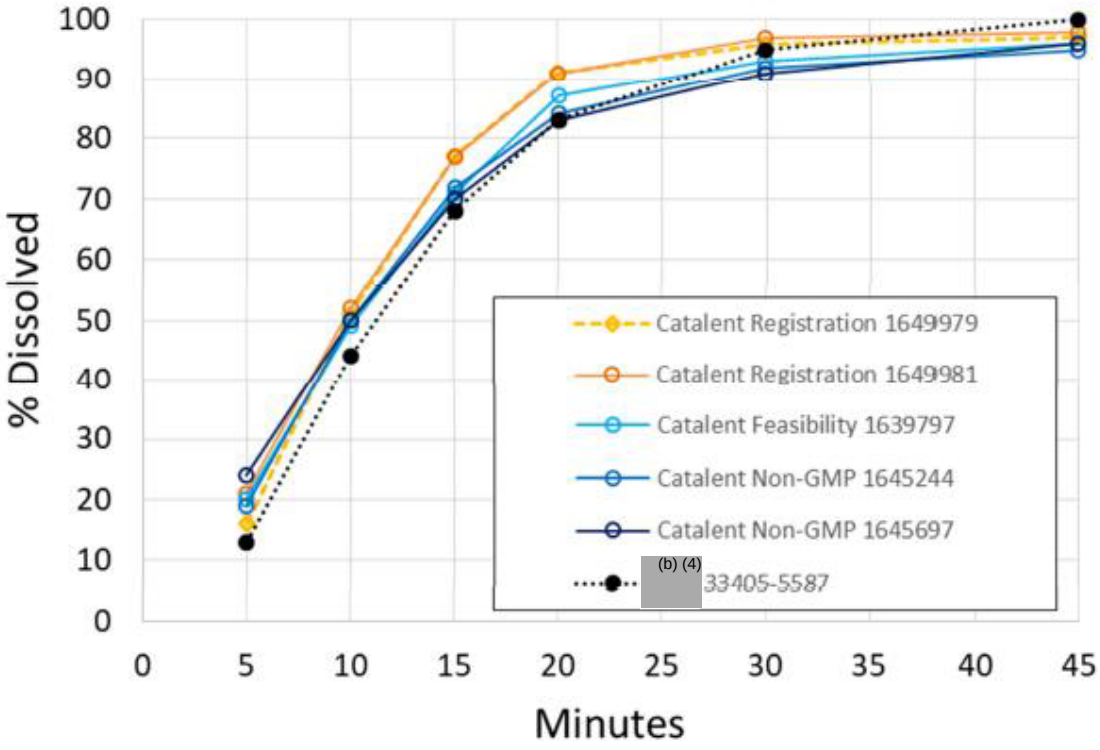
Table 7: Comparison of Dissolution of Tablets Manufactured at Two Sites

Manuf. Site	Lot Type	Lot No.	Date of Manufacture	F_2 Similarity Value (Catalent to (b) (4))	Age at Dissolution Testing
(b) (4)	Clinical Lot	33405-5587	(b) (4)	--	2 years
Catalent	Feasibility	1639797	Jan 2017	63	Newly Manufactured
	Confirmatory	1645244	Mar 2017	62	
		1645697		58	
	Registration	1649979	Apr 2017	57	
		1649981		54	

Note: F_2 values ≥ 50 indicate that the dissolution profiles may be considered similar

In their Response to IR dated 01/26/2018, the applicant provided complete dissolution data that allowed for the calculation of the f2 values in Table 7 by the reviewer. See Tables 13 through 17 in Appendix 1, below. For lot 1639797, f2 is 68.5. For lot 1645244, f2 is 68.5. For lot 1645697, f2 is 62.4. For lot 1649979, f2 is 61.2. For lot 1649981, f2 is 55.9. Although these f2 values differ from those reported by the applicant, in all five cases f2>50, so dissolution results are similar between the five Catalent lots and the (b) (4) lot. The comparative dissolution data demonstrate an adequate bridge of the manufacturing sites.

Figure 10: Dissolution Profiles for lofexidine Tablets Manufactured at Catalent and (b) (4)



These results show that the dissolution characteristics of tablets manufactured at both sites are similar.

Method Validation

In module 3.2.P.5.3 the applicant included Validation Report (b) (4) 2014-017. It stated that a qualification of the dissolution method was included in the original method transfer from (b) (4) in 2010, and then a complete method validation was performed by (b) (4) in 2014 since the original validation performed by (b) (4) did not meet current analytical standards. The applicant also included a dissolution method transfer from (b) (4) to Catalent (Table 8). Because these validation parameters focus on the HPLC method rather than the dissolution parameters, except as noted below, they will be assessed by the drug product reviewer.

Table 8: Summary of Dissolution Method Transfer (b) (4) to Catalent

Validation Parameters	Item	Acceptance Criteria	Results	Pass/Fail
System Suitability (Analyst 1)	(b) (4)			Pass
				Pass
				Pass
				Pass
				Pass
				Pass
System Suitability (Analyst 2)				Pass
				Pass
				Pass
				Pass
				Pass
				Pass
Linearity				Pass
Specificity				Pass
				Pass
Precision				Pass
				Pass
Intermediate Precision				Pass
				Pass
				Pass
References				

The Precision and Intermediate Precision results produced average dissolution values of (b) (4) with RSD values of 7%. These results are acceptable whether Q is set at (b) (4) or (b) (4)%. The low value of (b) (4) is acceptable for a Q value of (b) (4)% for Stage S_2 (n=12) testing, according to Dissolution <711>. Therefore, the dissolution results in this method transfer are adequate.

Bridging of Formulations

Reviewer's Assessment: N/A

Biowaiver Request

Reviewer's Assessment: ***N/A***

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date: Bryan Ericksen, Ph.D. 12/19/2017; 02/28/2018

Secondary Reviewer Name and Date: Kelly M. Kitchens, Ph.D., March 14, 2018

Appendix 1: Response to Information Requests (IR)

On February 16, 2018, in a response to the January 26, 2018 FDA information request, the applicant submitted the following information.

15. Submit the complete dissolution data [i.e. individual (n=12), mean, SD, % CV at each time point] for the dissolution profiles generated from the discriminatory power studies, i.e. the complete dissolution data from Figures 7-10 in your Dissolution Method Development Report.
16. Submit complete dissolution multi-point profile data for each variable tested during method development, assessment of discriminating ability, and validation [individual (n=12), mean, SD, % CV at each time point and mean profiles). Report the dissolution data as the cumulative percentage of drug dissolved (the percentage is based on the drug product's label claim). For the submission of the dissolution data, refer to data presentation below.

USWM Response (to Question 15 and 16):
As excel files cannot be included in the eCTD format, a "hard" exported PDF version of the data sets has been created and is provided in updated section 3.2.P.5.4. The requested Excel file with the profile dissolution data is provided as an attachment to the submission cover letter and an email to Dr. Stephen Kinsley, and "CC" to the RPM Kim Compton. This includes data from the dissolution method development report, release, and stability profiles for a single (b) (4) lot, and multiple lots from Catalent (Table 9).

Table 9: Dissolution Profile Data Provided in Excel File Format

17. Submit complete dissolution data for all (b) (4) and Catalent batches used to justify your proposed dissolution acceptance criterion. We recommend that you revise the dissolution acceptance criterion to the sampling time point where Q = (b) (4)% dissolution occurs, based on the average in vitro dissolution data of each batch/lot under study, equivalent to USP Stage 2 testing (n = 12).

USWM Response:
See Table 9 for the individual profile dissolution data available for (b) (4) and Catalent tablet batches. Dissolution results for drug product batches that were not tested in profile, but have n=6 dissolution results at 30 minutes only are summarized with average and low/high individual values in Table 10. This allows determination of the need to go to S2 testing. Tabular reporting of each individual value will be provided if requested.

Table 10: (b) (4) and Catalent 30 Minute Dissolution Values (Release and Stability)

Manuf.	Lot Number	Assessment Point (Months)[1]	30-minute Dissolution Values			Stage 2 Dissolution Testing	
			Average	Low	High	Q = (b) (4)	Q = (b) (4)
(b) (4)	94801-V5782	0	96	94	98		
		3	94	85	98		
		6	95	88	101		
		9	96	91	99		
		12	93	85	97		
		18	91	84	97		x
		24	93	82	102		x
		30	94	90	98		
		36	88	77	96	x	x
	94802-V5787	0	95	79	102	x	x
		3	95	87	100		
		6	97	95	102		
		9	97	88	101		
		12	93	86	101		
		18	89	82	97		x
		24	93	80	101		x
		30	92	82	98		x
		36	92	82	100		x
	94803-V5788	0	97	93	102		
		3	96	91	105		
		6	91	88	97		
		9	91	82	99		x
		12	91	85	101		
		18	91	81	99		x
		24	91	80	99		x
		30	90	80	96		x
		36	88	78	101	x	x
	24004-3545	0	95	83	107		x
		12	94	76	100	x	x
		18	94	90	99		
		24	91	85	95		
		30	96	88	105		
		36	95	86	101		
	33405-5588	Release	95	90	98		
	011015A	Release	92	84	102		x
Catalent	1639797	Release	93	82	100		x
	1645244	Release	95	88	98		
	1645697	Release	91	82	101		x
	1649979 (25°C)	0	96	87	103		
		1	96	93	99		
		3	97	87	104		
		6	95	87	101		
	(40°C)	1	95	89	100		
		3	92	85	99		
		6	84	74	94	x	x
	1649980	Release	96	92	100		
	1649981 (25°C)	0	97	87	104		
		1	95	87	101		
		3	95	86	101		
		6	100	95	103		
	(40°C)	1	95	92	101		
		3	92	77	99	x	x
		6[2]	47	38	56	N/A	N/A

Note: 'x' indicates that Stage 2 testing would be required at the listed Q value
[1] All stability data from tablets stored in proposed commercial packaging at 25°C/60%RH
[2] Suspected seal failure, data not representative of expected dissolution under these conditions

Regarding revision of the Q and evaluation time for the method, we agree that a Q of (b) (4)% at 30 minutes could be accommodated as a reasonable control for lofexidine tablets. In terms of dissolution results for lots at release, this control level would cause 2 of the Catalent lots to go to S2 testing (Figure 11):

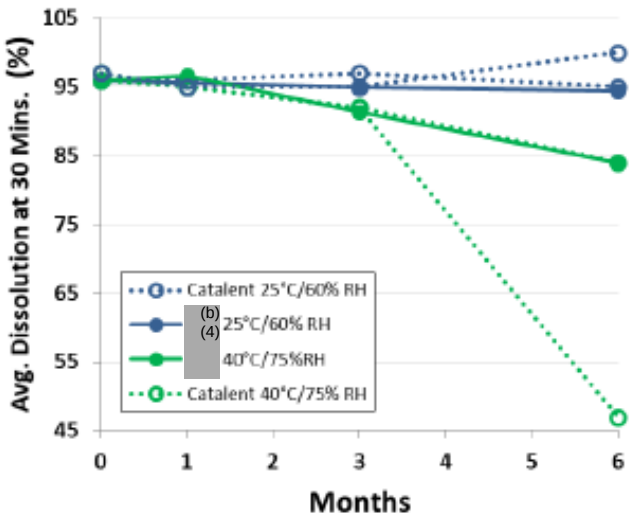
Figure 11: Mean Dissolution Profiles of (b) (4) Lot 33405-5588 and Catalent Lots at Release using a Q of (b) (4)%

Note: Error bars represent the individual high and low dissolution values at each time point.
Each time point represents the mean of 6 lots.

available on the Catalent lots is limited, making it more difficult to set appropriate controls at this time. Because of the lack of long-term data, dissolution from tablets stored at 40°C/75%RH are being presented here for additional context. USWM is concerned that the dissolution acceptance criteria do not get set too tight based on a preponderance of profile data from newly manufactured lots.

To consider the impact of adopting a Q value of (b) (4)% at 30 minutes on lofexidine tablet lots as they age, it is useful to note the similarity of dissolution behavior between the (b) (4) and Catalent lots (Figure 12). Aside from the stability outlier which was most likely attributable to a failed seal (the 40°C/75%RH 6 month pull for lot1649981), the average 30-minute dissolution results for (b) (4) and Catalent lots are comparable.

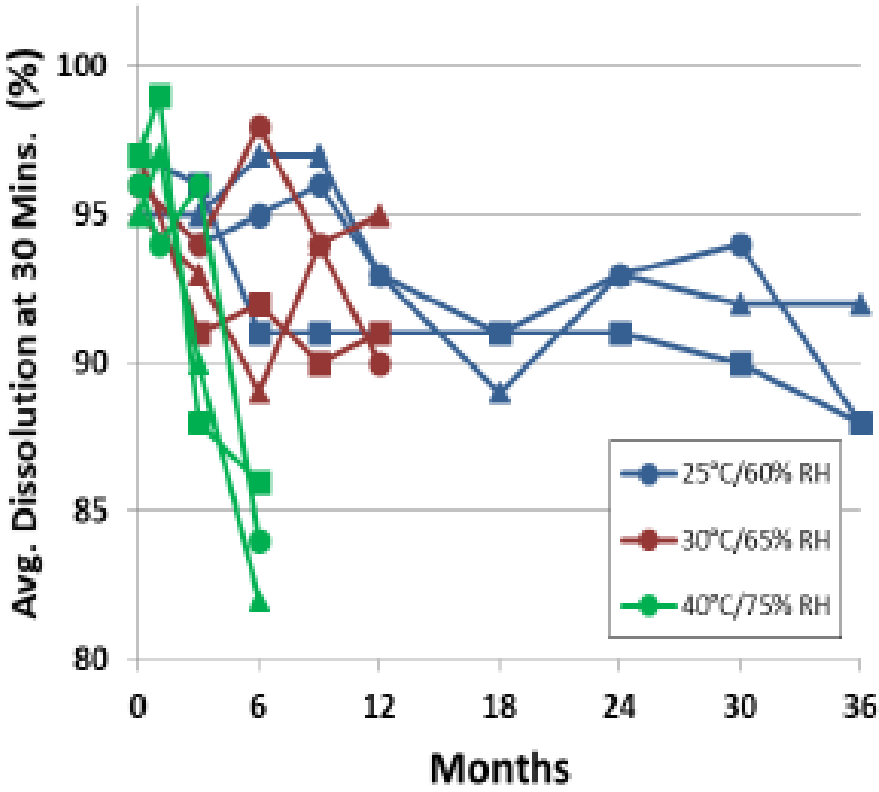
Figure 12: Comparison of (b) (4) and Catalent Dissolution Results on Stability



Note: The Catalent outlier was most likely attributed to a failed seal which affected appearance, water and hardness results for the same sample

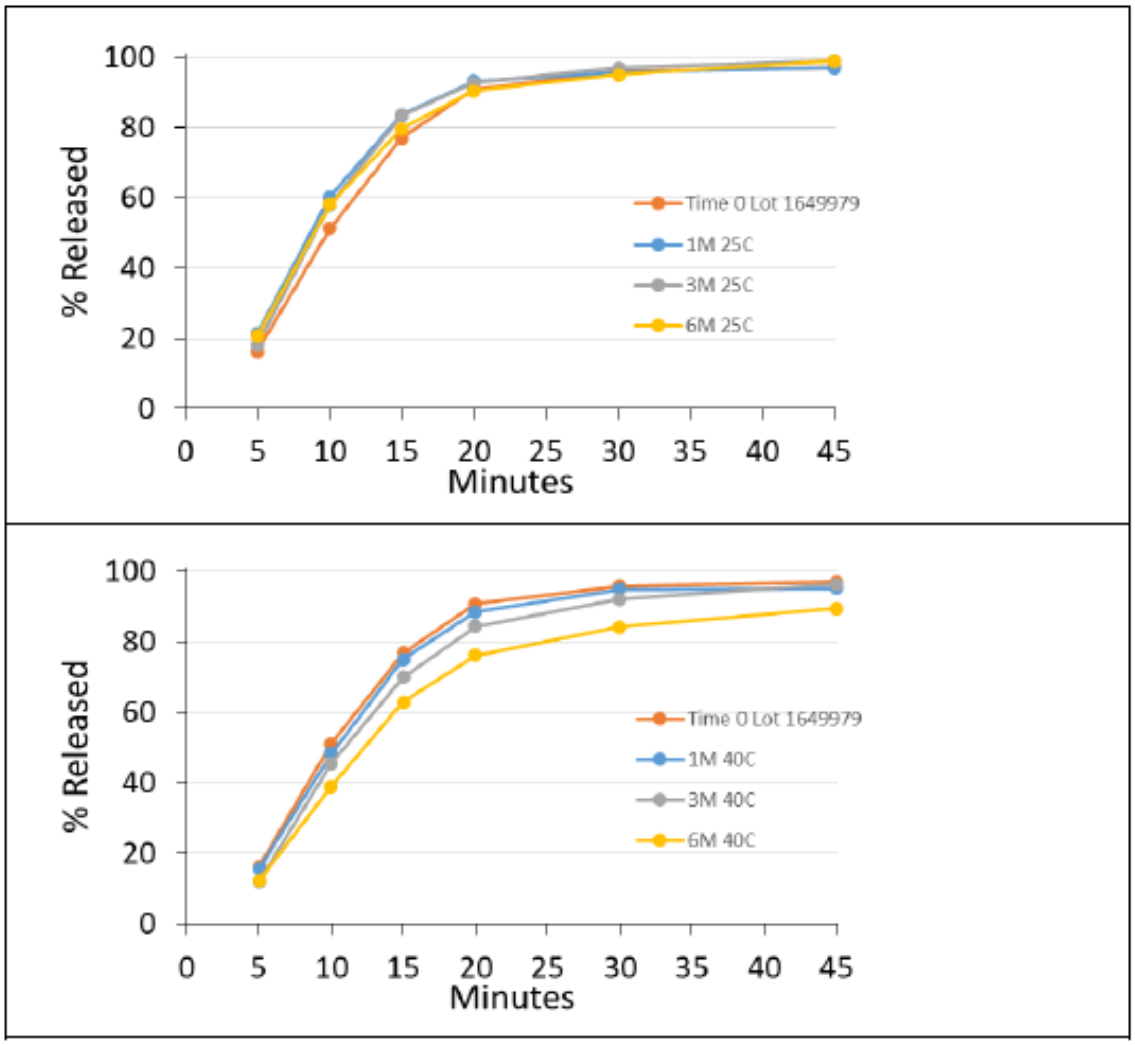
This leads us to consider the long-term (b) (4) data as likely being representative of what the dissolution data from the Catalent lots will look like as they age (Figure 13). In general, dissolution rate decreases with increased temperature and time.

Figure 13: Dissolution in (b) (4) Stability Lots



Representative data from Catalent Registration lot 1649979 shows that the dissolution rate is currently unaffected through 6 months storage at the long-term condition, but small time-dependent declines in the dissolution profile are apparent in tablets stored at 40°C/75% RH which is consistent with the (b) (4) data (Figure 14).

Figure 14: Stability Dissolution Profiles for Catalent Registration Lot 1649979 (25°C and 40°C Storage) through 6 months.



A summary of the 30-minute dissolution results from release and stability throughout development shows that adopting a Q of (b) (4)% using the existing dissolution method would likely result in a substantial increase in S2 testing especially at the later stability intervals (24 and 36-month testing) (Table 10).

Note that the outlier 6-month results from Catalent registration lot 1649981 stored at 40°C/75%RH clearly showed altered dissolution characteristics, along with changes in appearance, water, and hardness, providing another successful point of discrimination for the analytical method.

Taking the limited dissolution data set into consideration, USWM believes a Q of (b) (4)% with evaluation at (b) (4) minute time point meets the regulatory expectation for immediate release tablets, and will provide sufficient sensitivity so that a change in tablet performance will be detected. Section 3.2.P.5.1 and 3.2.P.5.6 have been updated accordingly. Updates to the Method to reflect the Q change from (b) (4)% to (b) (4)% will be provided subsequently.

18. Provide an explanation for the high variability observed at the early dissolution time points.

USWM Response:
Variability in the early timepoints of a dissolution profile is, of course, expected to some extent since the early points fall on the steep portion of the dissolution curve. The variability for lofexidine tables may be affected slightly more than other products due to a more variable initial interaction between the especially small, lightweight tablet and the paddle as the tablet dissolves. The tablet does not always sink to the bottom of the vessel immediately as dissolution begins, and this may contribute to varying release rates of the drug substance. The volume of dissolution medium (b) (4)
(b) (4)

Additional Comments Biopharmaceutics:
Dissolution Data Presentation: In the dissolution method development report and/or batch analysis section, present detailed experimental dissolution data as follows:
• In the narrative portion of the dissolution report, include individual vessel data as much as possible, particularly regarding investigation of selection of equipment, media, agitation speed, etc.
• In addition to the mean dissolution data presented in graphical and tabular formats, submit in the "Batch Analysis" section 3.2.P.5.4 of your NDA the individual vessel dissolution data for the batches of the proposed product used in the pivotal clinical/PK and registration/stability studies in Microsoft Excel ".xls or .xlsx" format. If available, include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.
• Provide in your NDA the dissolution data as described in the example below.

USWM Response:
As excel files cannot be included in the eCTD format, a "hard" exported PDF version of the data sets has been created and is updated in section 3.2. P.5.4. An email will be provided to Dr. Stephen Kinsley with the requested excel file, 'CC to the RPM Kim Compton. Individual tablet n=6 dissolution results at 30 minutes will be provided in tabular form for development and stability lots, if requested. All available dissolution profile data have been summarized in the Excel file.

Data from the Excel file:

Table 11: (b) (4) Lot 33405-5588, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	14	44	68	83	95	100
SD	4	8	9	10	6	3
% CV	31	18	13	12	6	3

Table 12: (b) (4) Lot 33405-5588, Heat and humidity-stressed, standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	29	61	83	89	93	95
SD	5	8	7	5	4	3
% CV	16	13	9	6	4	3

Table 13: Catalent Lot 1639797, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
Mean	20	49	71	87	94	96
SD	8	10	10	9	6	4
% CV	38	19	14	10	7	5

Table 14: Catalent Lot 1645244, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
Mean	19	50	72	84	92	96
SD	10	13	17	14	7	3
% CV	54	27	23	16	8	3

Table 15: Catalent Lot 1645697, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
Mean	24	51	70	83	91	96
SD	5	11	12	10	7	5
% CV	20	21	17	13	7	5

Table 16: Catalent registration batch 1649979 from T0 stability data, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	16	51	77	91	96	97
SD	10	11	11	7	4	3
% CV	61	22	14	8	4	3

Table 17: Catalent registration batch 1649981, from T0 stability data, Standard dissolution conditions

	5	10	15	20	30	45
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	21	55	78	91	97	98
SD	8	14	10	8	4	3
% CV	39	25	12	9	4	3

Bryan Ericksen

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Kelly Kitchens

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