CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

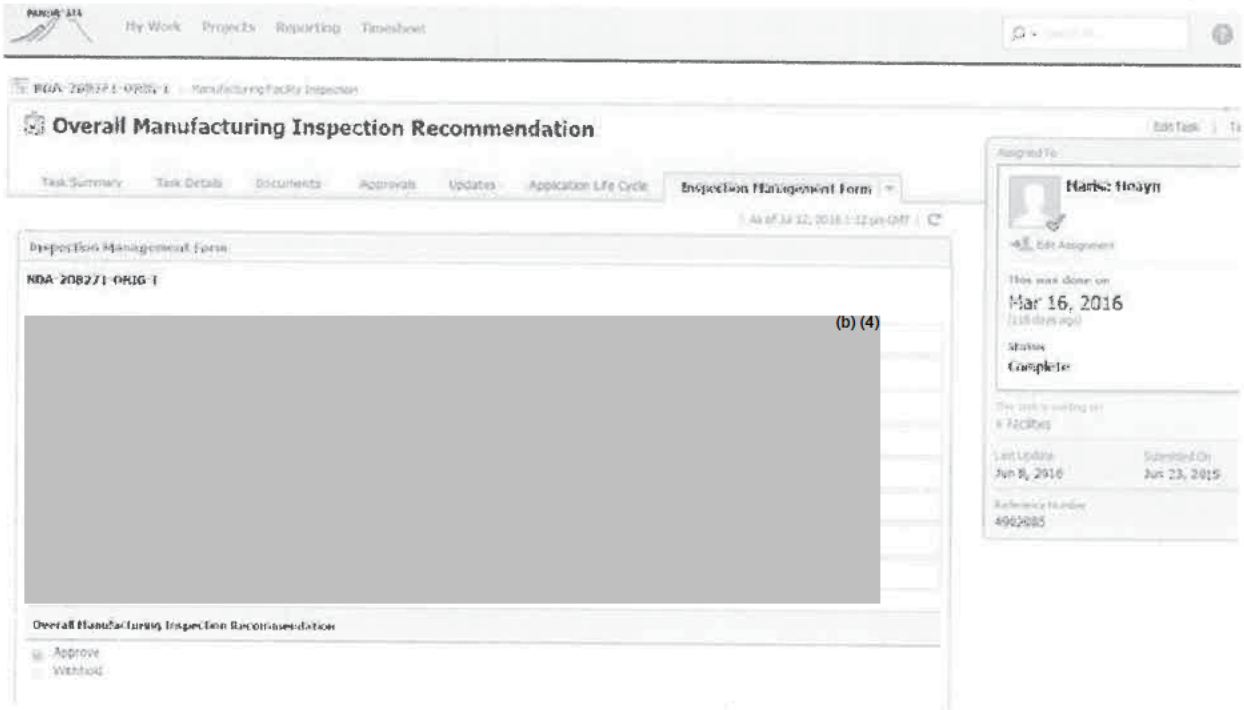
208271Orig1s000

CHEMISTRY REVIEW(S)

From: Quach, Truong
To: Allan, Lawrence
Subject: RE: NDA 208271 - RELISTOR - Final facilities inspection report
Date: Tuesday, July 12, 2016 1:15:13 PM

Hi Lawrence,

The overall manufacturing inspection recommendation remains APPOVABLE. Please see Panorama screen shot.



Thanks.

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Ave, Building 75, Room 4620
Silver Spring, MD 20993

From: Allan, Lawrence
Sent: Tuesday, July 12, 2016 1:09 PM
To: Quach, Truong
Subject: NDA 208271 - RELISTOR - Final facilities inspection report

Good afternoon Truong,

Please refer to the attached pages from the CMC review for this product. We're planning to take an approval action on this product next week and just want to confirm that there hasn't been any new information concerning these facilities, as it's been ~ 4 months since the CMC review was completed.

Please contact me if you have any questions.

Regards,

Lawrence Allan

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
ODE III | OND | CDER | FDA
10903 New Hampshire Ave.
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Silver Spring, MD 20993
Phone: (240) 402 – 2786 | E-mail: lawrence.allan@fda.hhs.gov

Recommendation:
This NDA is recommended for approval.

NDA 208271
Review #1

Drug Name/Dosage Form	Methylnaltrexone Bromide Tablets
Strength	150 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Salix Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	19-JUN-2015	CMC API
Amendment	25-NOV-2015	CMC API
Amendment	20-JAN-2016	CMC API
Original Submission	19-JUN-2015	Drug Product
Amendment	20 January, 2016	Drug Product
Amendment	12 December 2015	Drug Product
Amendment	24 February, 2016	Drug Product
Amendment	10 March, 2016	Drug Product labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sukhamaya (Sam) Bain	OMPT/CDER/OPQ/ONDP/DND API/NDBII
Drug Product	Sarah Ibrahim	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Process	Bo Jiang	OMPT/CDER/OPQ/OPF/DPAII/PABV
Microbiology	Bo Jiang	OMPT/CDER/OPQ/OPF/DPAII/PABV
Facility	Marisa Heayn	OMPT/CDER/OC/OMQ/DDQII/GCBIII
Biopharmaceutics	Vidula Kolhatkar	OMPT/CDER/OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Truong Quach	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Danuta Gromek-Woods	OMPT/CDER/OPQ/ONDP/DND PII/ NDPBV
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Sarah Ibrahim	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	29-AUG-2015	
	Type II			Adequate	15-OCT-2015	
	Type II			Adequate	27-DEC-2015	
	IV			Adequate	8/25/2015	Last reviewed by Raymond P. Frankewich, Ph.D. May 15, 2014 and no additional information has been submitted
	III			Adequate	8/25/2015	
	III			Adequate	8/25/2015	Olen M. Stephens, Ph.D. June 22, 2009 with no additional information submitted
	III			Adequate	8/25/2015	Gene W. Holbert, Ph.D. 02/03/2012 with no additional information submitted
	III			N/A		
	III			N/A		
	III			Adequate		KASLIWAL, RAVINDRA

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
		(b) (4)				K 10/01/2013 with no additional information submitted
(b) (4)	III			Adequate		MCLAMORE, SHERITA D 05/29/2014
	III			Adequate		BROWNEWELL, SHARON L 06/14/2010
	III			N/A		
	III			Adequate		KURTYKA, BOGDAN 04/17/2012 with no additional information submitted
	III			Adequate		AGARWAL, RAJIV 10/03/2007 with no additional information submitted
	III			N/A		
	III			N/A		

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67452	

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

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

Labeling/labels are deemed satisfactory from the CMC perspective.

The Office of Facility and Process has made a final overall manufacturing Inspection "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

Therefore, from the OPQ perspective, this NDA is recommended for approval.

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

N/A

II. Summary of Quality Assessments

Methylnaltrexone Bromide Tablets, 150 mg, have been developed to provide a new dosage form in addition to currently approved Relistor® (methylnaltrexone bromide) Subcutaneous (SC) Injection. This new oral 150-mg tablet formulation of Relistor was developed for patient convenience and ease of use in the treatment of OIC in the chronic non-cancer pain population.

A. Drug Substance, methylnatrexone bromide, Quality Summary

The active pharmaceutical ingredient in the drug product is methylnaltrexone bromide. The drug substance will be sourced from (b) (4), and Mallinckrodt, Inc. MO, USA. The detailed drug substance CMC information is provided in DMF (b) (4) and also two DMFs from Mallinckrodt: DMF (b) (4)) and DMF (b) (4)). These three DMFs were reviewed in support of this NDA by Dr. Sukhamaya (Sam) Bain, Ph.D. and found to be adequate.

Methylnaltrexone bromide) is a μ-opioid receptor antagonist. Its chemical name is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$ and the molecular weight is 436.36. Methylnatrexone

bromide is a white or almost white crystalline powder. It is soluble in water and in polar organic solvents, sparingly soluble in non-polar organic solvents. Aqueous solubility decreases with increasing pH, making the drug substance slightly soluble at pH 7.8-12.0. (b) (4)

The drug substances from (b) (4) and Mallinckrodt are produced (b) (4) however, the final drug substances are comparable based on submitted data, please refer to the review of Dr. Bain, pages 12-15 of this review. In addition, the comparability protocol for transferring the (b) (4) drug substance manufacturing from its own facility at (b) (4), to that of (b) (4) (a contract manufacturer) at (b) (4) was found satisfactory from the API quality review perspective.

Based on the drug substance quality assessment, the drug substance is controlled by adequate specifications that includes tests for appearance, identification, assay, impurities, (b) (4), water content, residue on ignition, loss on drying, residual solvents, specific optical rotation, (b) (4) content, particle size, (b) (4), pH (b) (4), and heavy metals. In addition, the Mallinckrodt specification includes also microbial limits.

For the drug substance from (b) (4) the drug substance is packaged in (b) (4)

The proposed re-test period is (b) (4) months for the (b) (4) drug substance and (b) (4) months for the Mallinckrodt drug substance, when stored at (b) (4) in the container closure system described above.

B. Drug Product, methylnatrexone bromide tablets, Quality Summary

RELISTOR immediate release tablets, 150 mg, are white, round, biconvex, film-coated tablets, debossed with "REL" on one side and plain on the other side. Inactive ingredients are silicified microcrystalline cellulose, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc. All excipients are deemed to be adequately controlled.

From the drug product review perspective, the RELISTOR's specification is acceptable to assure the identity, purity, strength, and quality. The testing includes appearance, identification, assay, impurities, and uniformity of dosage units, dissolution, (b) (4), and microbial limits. The submitted validated analytical procedures are deemed satisfactory.

From the biopharmaceutics perspective, the proposed dissolution method, acceptance criteria and method validation are acceptable. Since the tablet [redacted] (b) (4) exhibit rapidly-disintegrating and rapidly-dissolving attributes, traditional dissolution method employing the USP apparatus 2 (paddles) at a range of 50 rpm is justified. Since this drug product is expected to be completely dissolved in the stomach and the solubility of the drug substance does not vary considerably across the physiological pH range of 1.2 to 7.2, 0.1N HCl was considered the most relevant dissolution medium. Using 900 mL of this medium, the solubility of methylnaltrexone bromide is more than sufficient to establish sink conditions for the 150-mg drug product.

A BE study and dissolution testing in four media were conducted to provide link/bridging between the tablets manufactured by [redacted] (b) (4) and [redacted] (b) (4) (the proposed manufacturing process). Methylnatrexone bromide tablets manufactured by either process demonstrated rapid *in vitro* dissolution in all tested dissolution media, 0.1N HCl (QC media), pH 4.5 sodium acetate buffer, pH 6.8 sodium phosphate buffer and pH 7.4 sodium phosphate buffers.

According to the microbiology reviewer, Dr. Bo Jiang, Ph.D., Microbial limits test is included in the drug product specification, the test methods are in accordance with current USP <61> and USP <62>, and the acceptance criteria comply with USP <1111>, and are appropriate for a solid oral dosage form. The microbiology assessment overall recommendation is "Acceptable".

For commercial distribution, RELISTOR will be packaged in 6-, 60-, and 90-count high-density polyethylene bottles [redacted] (b) (4), and each bottle will include 2 silica gel desiccants. Based on assessment of the drug product reviewer, Dr. Sarah Ibrahim, the proposed container closure system is adequate to assure protection [redacted] (b) (4) to ensure the drug product stability. On the basis of the stability data provided, the 36-month expiration dating period is granted when the tablets are stored at up to 25ºC (77ºF).

The proposed drug product is manufactured by [redacted] (b) (4)

[redacted] (b) (4)

[redacted] The firm has stated that the source of drug substance did not have a meaningful impact on [redacted], tablet disintegration, friability, or dissolution. The firm also satisfactorily addressed control of particle size on request from FDA.

The Process reviewer, Dr. Bo Jiang, concludes that the process has been adequately defined and in-process controls are sufficient to ensure drug product quality.

In conclusion, RELISTOR® is recommended for approval from the drug substance, drug product, process, biopharmaceutics, microbiology, and facility perspective.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	RELISTOR
Non Proprietary Name of the Drug Product	Methylnaltrexone Bromide
Non Proprietary Name of the Drug Substance	Methylnaltrexone bromide is (R)-N-(cyclopropylmethyl) noroxymorphone methobromide
Proposed Indication(s) including Intended Patient Population	Treatment of Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain
Duration of Treatment	[redacted]
Maximum Daily Dose	450mg/day (3 x 150 mg)
Alternative Methods of Administration	None

The dosing regimen consists of a maximum three tablets per day.

The following ICH Q3B limits apply:

Drug Product	Reporting Thresholds (RT)	Identification Threshold (IT)	Qualification Threshold (QT)
Methylnaltrexone Bromide	[redacted]%	[redacted]	[redacted]

D. Biopharmaceutics Considerations

1. BCS Classification: N/A
   - Drug Substance:
   - Drug Product:

2. Biowaivers/Biostudies: N/A
   - Biowaiver Requests

- PK studies
- IVIVC

E. Novel Approaches: N/A

F. Any Special Product Quality Labeling Recommendations: N/A

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

This application is recommended for approval from the OPQ perspective.

Danuta Gromek-Woods, Ph.D.
CMC Lead/Application Technical Lead
14-Mar-2016

Danuta E. Gromek-woods -S

Digitally signed by Danuta E. Gromek-woods -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605430, cn=Danuta E. Gromek-woods -S
Date: 2016.03.16 10:14:23 -04'00'

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

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Satisfactory

Marisa Heayn, Consumer Safety Officer 02/29/2015

Marisa Heayn -S
Digitally signed by Marisa Heayn -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Marisa Heayn -S, 0.9.2342.19200300.100.1.1=2000327389
Date: 2016.03.16 09:03:48 -04'00'

Secondary Review Comments and Concurrence:

I concur with the overall recommendation.

Juandria Williams, PhD; DIA/B3
March 14, 2016

Juandria Williams -S
Digitally signed by Juandria Williams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000459158, cn=Juandria Williams -S
Date: 2016.03.16 08:08:37 -04'00'

ASSESSMENT OF THE BIOPHARMACUETICS

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

The applicant has proposed the following dissolution method and acceptance criteria for the proposed product:

Apparatus:	USP apparatus 2 (Paddles)
Temperature:	37.0 ± 0.5 °C
Rotation speed:	50 rpm
Dissolution media volume:	1000 mL
Dissolution medium:	0.1 N HCl
Sampling volume:	10 mL
Sampling time:	2, 5, 7, 10, 15, 20, 30 minutes Single Time Point: 15 minutes

The proposed Q value is (b) (4) % dissolved in 15 minutes

The drug substance, methylnaltrexone bromide, (b) (4) . The drug substance is freely soluble in water over physiological pH range 1.2 to 7.2.

Table 1: Solubility Profile of Methylnaltrexone Bromide at 25°C in Aqueous Phase

pH Range	Solubility Classification
3.4 to 6.0	Very soluble
6.2 to 7.0	Freely soluble
7.2 to 7.6	Soluble
7.8 to 12.0	Slightly soluble

Table 1: Comparison of Chemical Properties of Methylnaltrexone Bromide from Mallinckrodt and (b) (4)

Characteristics	(b) (4) (Lot P00882)	(b) (4) (Lot P05890)	(b) (4) (Lot 11P1136)
pKa	Mean (% RSD)		
LogD (estimated values)	(b) (4)		
LogP (estimated values)			
Intrinsic Dissolution Rate			
pH 1.2			
pH 4.5			
pH 6.8			
pH 7.2			
pH Solubility			
pH 1.2			
pH 4.5			
pH 6.8			
pH 7.2			
pH 8.4			
pH Stability (~1.2 mg/mL)			
pH 1.2			
pH 4.5			
pH 6.8			
pH 7.2			
pH 8.4			
(b) (4)			

Abbreviations: LogD = distribution coefficient, LogP = partition coefficient, pKa = dissociation constant, RSD = relative standard deviation.

[a] (b) (4) drug substance manufacturing process, currently approved in NDA 021964 for Relistor® (methylnaltrexone bromide) Subcutaneous Injection, was used predominantly during development of Methylnaltrexone Bromide Tablets.

[b] (b) (4) drug substance manufacturing process, used in the tablet NDA registration batches and approved for Relistor NDA 021964 on 03 February 2015, is the proposed commercial process.

(b) (4)

(b) (4)

Table 2: Partition Coefficient and Log P for Methylnaltrexone Bromide and (b) (4)

Sample	Partition Coefficient	Log P
Methylnaltrexone bromide	0.025	−1.605
(b) (4)		

After several changes the applicant selected (b) (4) tablet formulation.

Table 1: Components and Composition of Methylnaltrexone Bromide Tablets, 150 mg

Ingredient	Quality Standard	Function	Theoretical Quantity	
			mg/tablet	% w/w [a]
(b) (4)				
Methylnaltrexone bromide [b]	In house	Active	150.00	(b) (4)
Microcrystalline cellulose [c]	NF	(b) (4)		(b) (4)
Crospovidone	NF			
Edetate calcium disodium	USP			
Sodium lauryl sulfate	NF			
Colloidal silicon dioxide	NF			
Croscarmellose sodium	NF			
Poloxamer 407 (b) (4)	NF			
Silicified microcrystalline cellulose	NF			
Stearic acid (vegetable source)	NF			
(b) (4)				
Total Theoretical Weight:	---		533.59	100.0

Abbreviations: DMF = drug master file, NF = National Formulary, USP = United States Pharmacopeia, w/w = weight/weight.

(b) (4)

Dissolution method used at an earlier stage was modified in conjugation with changes in the drug product formulation. Prior to analysis of the NDA registration batches, the analytical procedure was modified as follows:

- The dissolution medium was changed from (b) (4) to 0.1N hydrochloric acid (HCl). Dissolution profile data showed no

meaningful differences in discrimination among various media so 0.1N HCl was selected as the most biorelevant medium.

- The time points for the dissolution profile were changed from [redacted] (b) (4) to 2, 5, 7, 10, 15, 20, and 30 minutes to provide a potentially more discriminating dissolution profile for the drug product.

The applicant provided the following justification for the method selection:

Methylnaltrexone Bromide Tablets, 150 mg, [redacted] (b) (4) exhibit rapidly-disintegrating and rapidly-dissolving attributes. Traditional dissolution methods for such drug products employ the use of USP apparatus 2 (paddles) at a range of 50 rpm to 75 rpm. Since this drug product is expected to be completely dissolved in the stomach and the solubility of the drug substance does not vary considerably across the physiological pH range of 1.2 to 7.2, 0.1N HCl was considered the most relevant dissolution medium. Using 900 mL of this medium, the solubility of methylnaltrexone bromide is more than sufficient to establish sink conditions for the 150-mg drug product.

To study the potential discriminating capabilities of the proposed dissolution method and to confirm the suitability of the chosen dissolution parameters, the dissolution of drug product batch KGZY (representing the proposed commercial formulation) was first evaluated using [redacted] (b) (4)

Using paddles at 50 rpm, full dissolution was demonstrated within ~10 minutes.

Comparative dissolution data in various media for the original [redacted] (b) (4) tablet formulation (manufactured via [redacted] (b) (4) used in phase 3 study MNTX 3201 as well as for the proposed commercial drug product formulation (manufactured via [redacted] (b) (4) used in clinical bridging studies MNPK1001 and MNOC1111 was evaluated (represented in the following table titled Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original [redacted] (b) (4) vs. Proposed [redacted] (b) (4) Drug Product). Overall, the in vitro release profiles for the original and proposed drug products were similar; at least 80% of the drug was released within 15 minutes for both formulations under all conditions tested.

Table 3: Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product

	Bulk Drug Product Batch Number			
	Medium / Dissolution (Mean % Released [n =12])			
Time Point (minutes)	0.1N Hydrochloric Acid			
	2010B0002 [a]	KNPZ [b]	KGZY [c]	NBMC [d]
2	73	52	82	77
5	89	84	94	89
7	93	91	98	92
10	96	95	101	94
15	97	97	102	96
20	98	98	103	97
30	98	98	103	98
Time Point (minutes)	pH 4.5 Sodium Acetate Buffer			
	2010B0002 [a]	KNPZ [b]	KGZY [c]	NBMC [d]
2	51	42	79	76
5	78	77	90	88
7	85	84	94	92
10	89	89	97	95
15	93	94	100	97
20	95	96	101	98
30	97	98	101	99
Time Point (minutes)	pH 6.8 Sodium Phosphate Buffer			
	2010B0002 [a]	KNPZ [b]	KGZY [c]	NBMC [d]
2	62	52	75	74
5	80	74	90	89
7	86	81	94	93
10	90	86	97	96
15	93	90	99	98
20	94	92	99	99
30	95	94	100	99

	Bulk Drug Product Batch Number			
	Medium / Dissolution (Mean % Released [n =12])			
Time Point (minutes)	pH 7.4 Sodium Phosphate Buffer			
	2010B0002 [a]	KNPZ [b]	KGZY [c]	NBMC [d]
2	48	47	75	78
5	73	71	90	92
7	81	78	94	95
10	86	84	97	97
15	90	89	98	99
20	91	92	98	99
30	93	94	99	100

[a] Batch 2010B0002 (uncoated) was used in phase 3 study MNTX 3201, as well as in phase 1 study MNPK 1118, which included a comparison of the pharmacokinetics of methylnaltrexone after a single dose of uncoated and film-coated drug product.

[b] Batch KNPZ (uncoated) is representative of the phase 3 drug product formulation and (b) (4) manufacturing process. This batch was used as the control formulation in study MNPK1001, which evaluated changes in both the relative amounts and types of functional excipients and changes in the manufacturing process.

[c] Batch KGZY (film coated) is representative of the proposed commercial drug product formulation and (b) (4) manufacturing process. This batch was manufactured with drug substance from (b) (4) and was used in study MNPK1001.

[d] Batch NBMC (film coated) is one of the NDA registration batches. It was manufactured with drug substance from Mallinckrodt, Inc.

All the formulations, Batch 2010B0002 (uncoated used in Phase 3 study MNTX 3201 and phase 1 study MNPK 1118), Batch KNPZ (uncoated, representative of the phase 3 drug product formulation and (b) (4) manufacturing process), Batch KGZY

(film coated, representative of the proposed commercial drug product formulation and (b) (4) manufacturing process) and Batch NBMC (film coated, NDA registration batch) dissolved very rapidly (≥ 85% dissolved in 15 minutes) in all tested dissolution media, 0.1N hydrochloric acid (QC media), pH 4.5 sodium acetate buffer, pH 6.8 sodium phosphate buffer and pH 7.4 sodium phosphate buffer.

There are two proposed drug substance manufactures Mallinckrodt, Inc. and (b) (4) Drug substance from Mallinckrodt is identified as either (b) (4) These drug substance sources produce drug substance with different particle size distibution (PSD). The results for PSD which theoretically may impact drug product performance, are summarized in the folowing table:

Table 4: Drug Substance Particle Size Distribution

Characteristic	Mallinckrodt (b) (4) (Lot P00882)	Mallinckrodt (b) (4) (Lot P05890)	(b) (4) (Lot 11P1136)
PSD by Laser			
D(0.1)			
D(0.5)			
D(0.9)			
PSD by Sieve Analysis			
% of Sample < 75 µm			
Mean Particle Size			

Source: ASRPT-148.

[a] (b) (4) drug substance manufacturing process, currently approved in NDA 021964 for Relistor® (methylnaltrexone bromide) Subcutaneous Injection, was used predominantly during development of Methylnaltrexone Bromide Tablets.

[b] (b) (4) drug substance manufacturing process, used in the tablet NDA registration batches and approved for Relistor NDA 021964 on 03 February 2015, is the proposed commercial process.

Batch 2010B002 contained Mallinckrodt (b) (4), batch NBMC contained Mallinckrodt (b) (4), and batches KNPZ and KGZY contained (b) (4) drug substance. The dissolution data (presented earlier, in the table titled Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product) demonstrated that the drug substance particle size did not impact the release of methylnaltrexone bromide from the drug product.

As mentioned earlier all the batches batch 2010B002 (Mallinckrodt (b) (4) batch NBMC (Mallinckrodt (b) (4)) and batches KNPZ and KGZY ((b) (4) drug substance) demonstrated very rapid dissolution in all the dissolution media tested. Particle size does not impact release of methylnaltrexone bromide from the drug product. Therefore, based on the internal guidance of Division of Biopharmaceutics, the data provided support both the proposed drug substance manufactures.

The applicant has provided complete dissolution data for three registration batches, MXYS, NBMB, and NBMC).

Bulk Drug Product Batch Number	Tests and Acceptance Criteria: Dissolution Q = (b) (4) % dissolved in 15 minutes (in 0.1N HCl)							
	Vessel #	2 min	5 min	7 min	10 min	15 min	20 min	30 min	45 min [c]
MXYS	1								(b) (4)
	2								
	3								
	4								
	5								
	6								
	Mean	79	91	94	96	98	98	99	100
	% RSD	5.2	1.8	1.2	0.9	0.9	0.9	0.9	1.3
	Range								(b) (4)
NBMB	1								(b) (4)
	2								
	3								
	4								
	5								
	6								
	Mean	78	88	91	93	95	96	97	101
	% RSD	6.9	5.4	4.9	4.4	3.8	3.4	3.0	1.9
	Range								(b) (4)

Bulk Drug Product Batch Number	Tests and Acceptance Criteria: Dissolution Q = (b) (4) % dissolved in 15 minutes (in 0.1N HCl)							
	Vessel #	2 min	5 min	7 min	10 min	15 min	20 min	30 min	45 min [c]
NBMC	1								(b) (4)
	2								
	3								
	4								
	5								
	6								
	Mean	80	90	94	96	98	99	100	103
	% RSD	3.8	3.4	3.1	2.8	2.6	2.6	2.4	1.9
	Range								(b) (4)

c (b) (4)

Dissolution results for Methylnaltrexone Bromide Tablets, 150 mg, met the proposed specification after storage for 24 months at 25ºC/60% RH and 6 months at 40ºC/75% RH, and no trends were observed under either storage condition. On long-term stability, mean results through 24 months ranged from (b) (4) % dissolved (mean, 98%; SD, 1.9%) at 15 minutes; individual results ranged from (b) (4) % dissolved at 15 minutes.

The applicant conducted a DoE to study the effects of (b) (4) on the overall physical and in vitro performance attributes of the resulting Methylnaltrexone Bromide Tablets, 150 mg. The (b) (4) used for the drug product registration batches was (b) (4) and the (b) (4) was (b) (4) (b) (4)

While (b) (4) used to manufacture the registration batches, the 2 factors evaluated in the (b) (4) DoE were as follows:

- (b) (4)
- (b) (4)

(b) (4) The Applicant has stated that all of the results were consistent with both theoretical and prior knowledge gained from the drug product. This will be reviewed in details by process reviewer Dr. Bo Jiang.

The following Information Request (IR) was communicated to the Applicant on February 22, 2016:
The registration batches demonstrate complete dissolution at 30 min, therefore, the last dissolution time point ([redacted] (b) (4)) will not be needed and should be removed. We request that you acknowledge your acceptance of this recommendation. Also, update Module 32P51 Drug Specifications and other related sections for consistency.

The Applicant responded on February 24, 2016 and accepted the recommendation.

The Applicant provided the following response:

This is to confirm acceptance of the recommendation to remove testing at the last dissolution time point ([redacted] (b) (4))
The 3.2.P.5.1 Specification is not impacted by this recommendation because the release and stability acceptance criteria for dissolution is "Q = [redacted] (b) (4)% dissolved in 15 minutes."
The only impacted section to the current NDA is 3.2.P.8.3 Stability Data, whereby the following footnote #7 was added to each long-term stability data table (storage at 25°C/60% RH) to remove future testing for dissolution [redacted] (b) (4):

Testing for Dissolution at [redacted] (b) (4) will not be further performed at the request of the FDA per CMC Amendment submitted on 24Feb2016.

Method validation:
The following table represents chromatographic conditions used for analysis of dissolution samples:

CHROMATOGRAPHIC CONDITIONS

Column:	Waters, Symmetry C-18, 5 µm, 150 x 4.6 mm or equivalent
Column temperature:	30°C
Detection:	UV @ 220 nm
Injection Volume:	10 µL
Flow Rate:	1.0 mL/min
Run time:	8 minutes
Mobile Phase:	Methanol: Water: TFA 200: 800: 1 (v/v)

The following table represents a summary of method validation parameters evaluated:

Test	Acceptance criteria	Observation
System Suitability	Injection reproducibility % RSD should be ≤ 2%, the number of theoretical plates from the first injection should be ≥ 1000,	The acceptance criteria for system suitability of all sequences have been met.

<table>
<tr><td></td><td>tailing factor from the first injection should be ≤ 2.0, % recovery for check standard solution should be within 98% to 102%, % recovery of the system drift injection should be within 98% to 102%,</td><td></td></tr>
<tr><td>Filter bias</td><td>% Recovery should be within 97% to 103%. Interference should be ≤ 1%.</td><td>A (b) (4) filter was evaluated by making one injection of filtered and centrifuged sample solution. One injection of unfiltered and filtered dissolution medium was also made.
Table 2: Filter Bias Results
(b) (4)</td></tr>
<tr><td>Linearity and range</td><td>The correlation coefficient (r) should be ≥ 0.99. Report the slope, Y-intercept and the residual sum of squares from the plot.</td><td>The dissolution procedure is linear from the concentration range of 78.65 µg/mL to 188.8 µg/mL, which is equivalent to 50-120% of the nominal standard and sample concentration. All acceptance criteria were met for linearity. The range of the method was defined as 50-120%.</td></tr>
<tr><td>Specificity</td><td>There should be no peaks (at retention time of MNTX in working standard solution) > 2% of average peak area of MNTX from five injections of working standard appearing on the chromatograms of the placebo sample solution and dissolution medium at the retention time of active.</td><td>No peaks were detected at the retention time of MNTX in the placebo and dissolution medium injections.
Table 4: Specificity Results
Reference: Notebook PDS-NB-9522, pg. 121
<table><tr><th>Injection</th><th>Interference</th></tr><tr><td>Placebo sample Solution</td><td>None</td></tr><tr><td>Dissolution Medium</td><td>None</td></tr></table></td></tr>
<tr><td>Accuracy</td><td>The individual % Recovery of MNTX should be within 95% - 105% for all the samples at each level.</td><td>The method meets the acceptance criteria for accuracy study.
Table 5: Accuracy Study Results
Reference: Notebook PDS-NB-9522, pgs.122
<table><tr><th>SPL #</th><th>Spiking Level (%)</th><th>% Recovery</th><th>Mean % Recovery</th><th>% RSD</th></tr><tr><td>1</td><td rowspan="3">50</td><td>101.3</td><td rowspan="3">101.1</td><td rowspan="3">0.3</td></tr><tr><td>2</td><td>101.2</td></tr><tr><td>3</td><td>100.8</td></tr><tr><td>1</td><td rowspan="3">100</td><td>101.4</td><td rowspan="3">102.0</td><td rowspan="3">0.5</td></tr><tr><td>2</td><td>102.3</td></tr><tr><td>3</td><td>102.3</td></tr><tr><td>1</td><td rowspan="3">120</td><td>102.0</td><td rowspan="3">101.9</td><td rowspan="3">0.7</td></tr><tr><td>2</td><td>102.6</td></tr><tr><td>3</td><td>101.2</td></tr></table></td></tr>
<tr><td>Repeatability</td><td>The RSD for the % release values of six samples at 15 minutes time point should be ≤ 10%.</td><td>This method meets the acceptance criterion for repeatability study.</td></tr>
<tr><td>Intermediate precision</td><td>The RSD for the % release values of six samples at 15 minutes time point should be ≤ 10%. The absolute</td><td>This method meets the acceptance criteria for intermediate precision study.</td></tr>
</table>

	difference between the two mean % release values from the results generated by two analysts should be ≤ 10% at the time points with less than 85% dissolved, and should be ≤ 5% at the time points with 85% and above dissolved (all individual value should be 85% or above).	
Stability of Standard and Sample Solutions	The concentration of MNTX in the working standard and sample solution is within the range of 98% - 102% of the initial value.	The working standard solution is stable for up to 4 days at room temperature and under refrigeration (2-8 °C) both, protected or unprotected from light. The sample solution Is stable up to 4 days at room temperature and under refrigeration (2-8 °C) both, protected and unprotected from light.
Robustness	The % target should be within 98.0% to 102.0% for Robustness of HPLC Method. The Mean % of target should be within 90% to 110% at the time points with less than 85% dissolved and within 95% to 110% at the time points with 85% and above dissolved.	The HPLC Method is robust for moderate changes in Mobile Phase composition, Column Temperature and Flow rate. The Dissolution Method is robust for moderate changes in normality of dissolution medium, un-degassed dissolution medium and sink condition.

Reviewer's Assessment: Adequate.

The proposed dissolution method, acceptance criteria and method validation are acceptable from the biopharmaceutics perspective.

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

Several formulations were tested during the product development.

Figure 1: Summary of Dosage Forms and Manufacturing Processes

The following table represents a side-by-side comparison of the phase 3 and to-be-marketed formulations (with bridging studies noted therein). The Agency discussed the possible need for bridging studies with the applicant at pre-NDA meeting (IND 67452 pre-NDA meeting preliminary comments dated October 31, 2014). The applicant conducted PK bridging studies comparing different formulations. These studies will be reviewed by clinical pharmacology reviewer.

Table 1: Comparison of Phase 3 and Proposed Commercial Formulations

Clinical Use [a]	PHASE 3 FORMULATION MNTX 3201 (Phase 3 Study) MNPK 1118, MNPK1001, and MNOC111 (Bridging Studies)		PROPOSED COMMERCIAL FORMULATION MNPK1001 and MNOC1111 (Bridging Studies)	
Manufacturing Process	(b) (4)			
Components (Listed by Functionality)	**Theoretical Quantity**		**Theoretical Quantity**	
	mg/tablet	**% w/w**	**mg/tablet**	**% w/w**
Active Ingredient				
Methylnaltrexone bromide	150.00	(b) (4)	150.00	(b) (4)
(b) (4)				
Silicified microcrystalline cellulose	(b) (4)		(b) (4)	
Microcrystalline cellulose				
(b) (4)				
(b) (4)				
Croscarmellose sodium				
Crospovidone (b) (4)				
(b) (4)				
Sodium lauryl sulfate				
(b) (4)				
Poloxamer 407 (b) (4)				
(b) (4)				
Edetate calcium disodium				
(b) (4)				
Talc				
Colloidal silicon dioxide				
(b) (4)				
(b) (4)				
Stearic acid				
(b) (4)				
Total Theoretical Weight	533.59 [b]	100.0	533.59	100.0

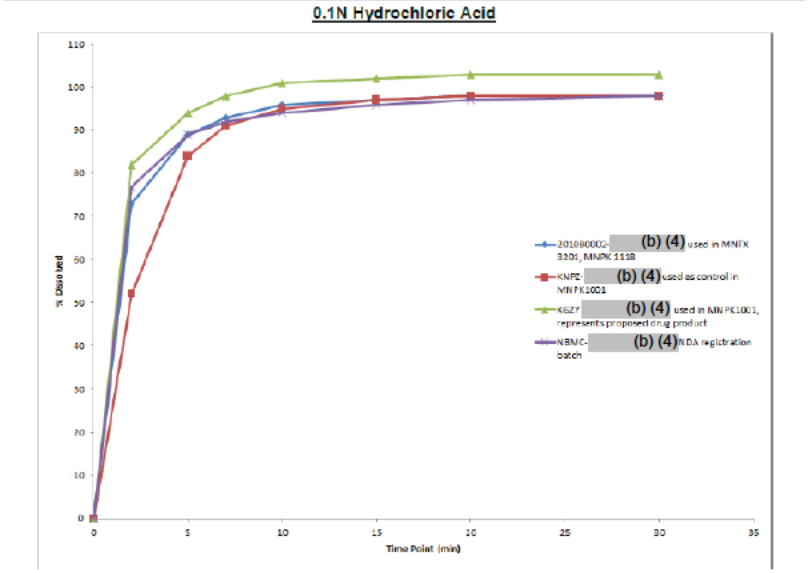
[a] Refer to Attachment 3 (b) (4) and Attachment 4 ((b) (4) for a complete list of clinical studies in which these formulations were used.

[b] Tablets used in phase 3 study MNTX 3201 were uncoated. Coated and uncoated tablets using the same (b) (4) formulation were compared in MNPK 1118, a phase 1 pharmacokinetic study. Uncoated tablets were also used in MNOC1111.

[c] (b) (4)

The following figures represent comparative dissolution of methylnaltrexone bromide tablets Batch 2010B0002 (uncoated (b) (4) batch used in study MNTX 3201), Batch KNPZ (uncoated (b) (4) batch used in study MNPK1001), Batch KGZY (film-coated (b) (4) batch used in study MNPK 1001, represents proposed drug product), NBMC (registration batch) in 0.1 N HCl (QC media), pH 4.5 sodium acetate buffer, pH 6.8 sodium phosphate buffer and pH 7.4 sodium phosphate buffer.

Figure 2: **Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product**



The above dissolution medium using 0.1N HCl is the proposed medium seeking approval.

Figure 2: **Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product (Cont'd)**

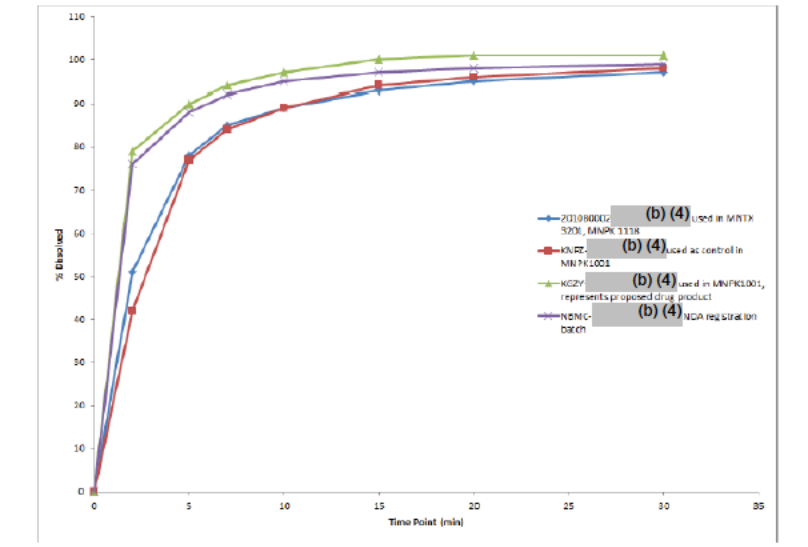


Figure 2: Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product (Cont'd)

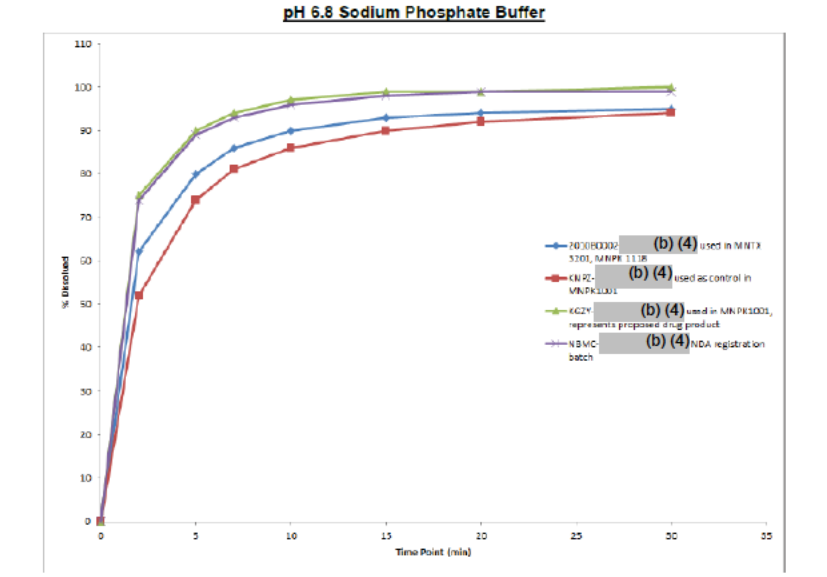
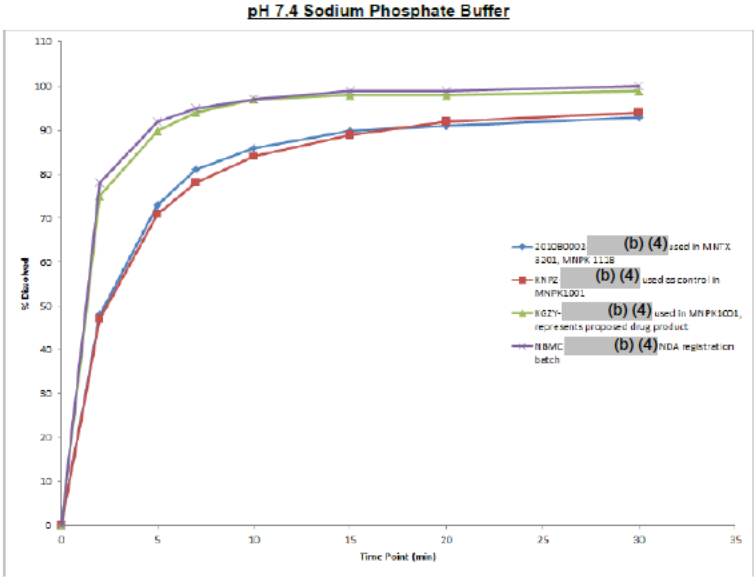


Figure 2: Comparative Dissolution of Methylnaltrexone Bromide Tablets, 150 mg, in Various Media—Original (b) (4) vs. Proposed (b) (4) Drug Product (Cont'd)



Reviewer's Assessment:

A BE study and dissolution testing in 4 media were conducted to provide link/bridging between the tablets manufactured by (b) (4) and (b) (4) processes (the proposed manufacturing method). Methylnaltrexone Bromide Tablets, 150 mg, manufactured by (b) (4) and

proposed (b) (4) demonstrated rapid in vitro dissolution in in all tested dissolution media, 0.1N hydrochloric acid (QC media), pH 4.5 sodium acetate buffer, pH 6.8 sodium phosphate buffer and pH 7.4 sodium phosphate buffer.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: Adequate.

From the Biopharmaceutics perspective,
1. The proposed dissolution method and acceptance criterion
2. The assay method and the validation report
are reviewed here and found acceptable to support the approval of this NDA.

NDA 208271 is recommended for approval from biopharmaceutics perspective.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
03/09/2016

Vidula R. Kolhatkar -S
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Date: 2016.03.15 15:03:16 -04'00'

Secondary Review Comments and Concurrence:

I concur 03/09/16

Tien-Mien Chen, Ph.D.

Acting Biopharm Lead

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ASSESSMENT OF MICROBIOLOGY

19. 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.

Specification:		
	Total aerobic microbial count:	NMT (b) (4) cfu/g
	Total combined yeasts and molds count:	NMT (b) (4) cfu/g
	Escherichia coli:	(b) (4)

Microbial limits are determined in accordance with current USP <61> and USP <62>. The acceptance criteria are appropriate for a solid oral dosage form.

Reviewer's Assessment: Acceptable.

Microbial limits test is included in the drug product specification, the test methods are in accordance with current USP <61> and USP <62>, and the acceptance criteria comply with USP <1111> and are appropriate for a solid oral dosage form.

The firm states that microbial enumeration testing is performed at the time of drug product release and annually on stability in 3.2.P.2.5. Stability protocol for both the registration batches and commercial batches specify MLT test on initial, 12M, 24M, 36M, 48M and 60M.

Stability data up to 18M have been provided, and the product complies with MLT requirement.

Assessment: Acceptable.
The drug product is proposed to be manufactured via a (b) (4) process. (b) (4) in the finished drug product is controlled at NMT (b) (4)% and is observed in the registration batches varied from (b) (4)% and not increasing on stability. The risk of microbial growth is low. In addition, the firm performs the MLT in product release testing, and the MLT test is also performed annually on stability batches. The microbial control on the drug product is adequate.

2.3.P.6 Reference Standards or Materials

20. 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:

Not applicable for oral solid drug product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

21. 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:

Refer to drug product review section.

22. 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: Acceptable.

None of the excipients used is of human or animal origin. The stearic acid used in the drug product is of vegetable origin.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The application is adequate in microbiology review.

Reviewer: Bo Jiang, Ph.D. / 10/8/2015

Bo Jiang -S

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Supervisor Comments and Concurrence:

I concur, the microbiology assessment overall recommendation is acceptable.
Celia N. Cruz, Ph.D. 11-03-2015
Acting Branch Chief, OPF/DPAII/BV

Celia Cruz -S

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

    The applicant submitted claim for categorical exclusion from the preparation of an environmental assessment for Methylnaltrexone Bromide Tablets, 150 mg.

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

    The expected introduction concentration (EIC), as defined in the Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications, July 1998, for methylnaltrexone bromide will be (b) (4) ppb which is below 1ppb.

Applicant's Response:

Reviewer's Assessment:

The cited categorical exclusion at 21 CFR 25.31 (a) is appropriate for the submitted application since no increase in use of active moiety is expected. The claim for categorical exclusion is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
The cited categorical exclusion at 21 CFR 25.31 (a) is appropriate for the submitted application and therefore the claim for categorical exclusion is acceptable.

NDA 208271 is recommended for approval from Environmental assessment

perspective.

Sarah Ibrahim, PhD
Reviewer, Branch V/DNDP II
ONDP

Sarah Ibrahim -S

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Date: 2016.03.15 17:31:23 -04'00'

Secondary Review Comments and Concurrence:
I concur.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

Moojhong Rhee -S

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

Labeling & Package Insert

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: RELISTOR® Established Name: Methylnaltrexone bromide	Proprietary name is presented correctly. The established name is presented correctly with a salt form because this active ingredient was approved before May 1, 2013. **Satisfactory.**
Dosage form, route of administration	Dosage: Tablets Route: Oral	The dosage form "Tablets" is described adequately. **Satisfactory.**
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablet: 150 mg	The strength of the tablet is expressed based on active moiety. An equivalency statement should be included. **Unsatisfactory.**

Conclusion:

1- Proprietary name RELISTOR® has been accepted and package insert includes the correct proprietary name and established name with retention of salt since this active ingredient was approved before May 1, 2016.

2- The dosage form is clearly described and adequately summarized.

However, since the established name is expressed as a salt form, an equivalency statement should be included in the Dosage Forms and Strengths section to reflect the amount of active moiety.

This section is **Unsatisfactory**

(b) "Full Prescribing Information" Section

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

As of 10/22/2015 eCTD (0009)

Tablets:

- 150 mg film-coated, white, round, biconvex, debossed with "REL" on one side and plain on the other side.

Injection:

Single-dose Vial:

- 12 mg/0.6 mL colorless to pale yellow solution

Single-dose Pre-filled Syringe:

- 8 mg/0.4 mL colorless to pale yellow solution
- 12 mg/0.6 mL colorless to pale yellow solution

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	3 DOSAGE FORMS AND STRENGTHS Tablet: • 150 mg supplied as white, round, biconvex, film coated tablets, debossed with "REL" on one side and plain on the other side. Single-use Vial: • 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe • 12 mg/0.6 mL solution for subcutaneous injection, with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs Single-use Pre-filled Syringe: • 8 mg/0.4 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard • 12 mg/0.6 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard	Consistent with Module 3.2.P.5.1, Specifications, Table 1 The Single use Vial and Single use pre Filled syringe are consistent with approved NDA 021964 Prescribing Information, as of September 2014 **Satisfactory.**
Strengths: in metric system	150 mg	The strength of the tablet is

		expressed based on the active moiety and therefore, an equivalency statement should be included to follow the CDER salt policy. **Unsatisfactory.**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	tablet supplied as white, round, biconvex, film coated tablets, debossed with "REL" on one side and plain on the other side.	The description of the tablet is concise and accurate. **Satisfactory.**

Conclusion:

1. The description of the identifying characteristics of the tablet dosage form, including container description, color and consistency is adequately expressed.

2. **The strength of the tablet should include an equivalency statement to reflect the amount of active moiety.**

This section is **Unsatisfactory.**

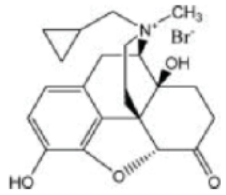
#11: Description (21CFR 201.57(c)(12))

As of 10/22/2015 eCTD (0009)

11 DESCRIPTION

RELISTOR® (methylnaltrexone bromide) is a mu-opioid receptor antagonist. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$ and the molecular weight is 436.36.

The structural formula is:



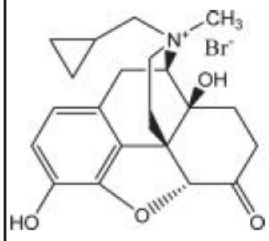
RELISTOR tablets for oral administration are film-coated and contain 150 mg of methylnaltrexone bromide. Inactive ingredients are silicified microcrystalline cellulose, microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

RELISTOR for subcutaneous administration is a sterile, clear and colorless to pale yellow aqueous solution. Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Each 8 mg/0.4 mL pre-filled syringe (1 mL syringe) contains 8 mg of methylnaltrexone bromide in 0.4 mL of water. The excipients are 2.6 mg sodium chloride USP, 0.16 mg edetate calcium disodium USP, and 0.12 mg glycine hydrochloride.

Each 12 mg/0.6 mL pre-filled syringe (1 mL syringe) contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	RELISTOR® (methylnaltrexone bromide)	Proprietary name is correct. The established name is also presented correctly. **Satisfactory.**
Dosage form and route of administration	RELISTOR tablets for oral administration	The dosage form and route are expressed correctly. **Satisfactory.**
Active moiety expression of strength with equivalence statement for salt (if applicable)	150 mg of methylnaltrexone bromide	The strength is expressed based on the active ingredient, and therefore an equivalency statement should be included to follow the CDER salt policy. **Unsatisfactory.**
Inactive ingredient information (quantitative, if injectables	Inactive ingredients are silicified microcrystalline cellulose,	The inactive ingredients information is presented

21CFR201.100(b)(5)(iii)), listed by USP/NF names.	microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, crospovidone, poloxamer 407, stearic acid (vegetable source), colloidal silicon dioxide, edetate calcium disodium, polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.	correctly. **Satisfactory.**
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	mu-opioid receptor antagonist	This will be determined in the labeling meeting.
Chemical name, structural formula, molecular weight	Chemical name for methylnaltrexone bromide is (R)-N-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is C21H26NO4Br and the molecular weight is 436.36. The structural formula is: 	The chemical names and the structural formula are correct. The molecular weight is included. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	NA	NA

Conclusion:

1. The chemical structures and formula are expressed correctly.
2. **The strength of the dosage form needs an equivalency statement to express the amount of active moiety per CDER salt policy.**
3. The molecular weight of the drug substance is included.
4. [redacted] (b) (4) listed as individual components as follows; polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc.

This section is **Unsatisfactory.**

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

As of 10/22/2015 eCTD (0009)

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NDC NUMBER	PACK SIZE	CONTENTS
65649-150-60	60-count bottle	85-(b)(4) bottle containing 60 tablets and 2 silica gel desiccant canisters. Each 150 mg film-coated tablet is white, round, biconvex, and debossed with "REL" on one side and plain on the other side
65649-150-90	90-count bottle	100-(b)(4) bottle containing 90 tablets and 2 silica gel desiccant canisters. Each 150 mg film-coated tablet is white, round, biconvex, and debossed with "REL" on one side and plain on the other side
65649-551-02	1 vial per carton	one 12 mg/0.6 mL single-use vial containing a colorless to pale yellow solution
65649-552-04	7 pre-filled syringes per carton	seven 8 mg/0.4 mL single-use pre-filled syringes with needle guard system containing a colorless to pale yellow solution
65649-551-03	7 pre-filled syringes per carton	seven 12 mg/0.6 mL single-use pre-filled syringes with needle guard system containing a colorless to pale yellow solution
65649-551-07	1 pre-filled syringe per carton	one 12 mg/0.6 mL single-use pre-filled syringe with needle guard system containing a colorless to pale yellow solution

Storage

Tablets

Store at up to 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Injection

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. **Do not freeze. Protect from light.**

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	150 mg	The strength needs an equivalency statement should be included to follow the CDER salt policy. **Unsatisfactory.**
Available units (e.g., bottles of 100 tablets)	85 (b)(4) bottle containing 60 tablets and 2 silica gel desiccant canisters. 100 (b)(4) bottle containing 90 tablets and 2 silica gel desiccant canisters.	The information provided is Adequate. **Satisfactory.**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	film-coated tablet is white, round, biconvex, and debossed with "REL" on one side and plain on the other side	The information provided is Adequate. **Satisfactory.**
Special handling (e.g., protect from light, do not freeze)	NA	Statement is present as **Do not freeze. Protect from light.** Only for Injection dosage form.
Storage conditions	Store at up to 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature].	The information provided is Adequate. **Satisfactory.**

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Salix Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA Under license from: Progenics Pharmaceuticals, Inc., Tarrytown, NY 10591	**Satisfactory.**

Conclusion:

1. **The strength of the dosage form needs an equivalency statement to reflect the amount of active moiety per CDER salt policy.**

2. Section 16 includes Available units, Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number, Special handling (e.g., protect from light, do not freeze) and Storage conditions.

3. The package insert section 17 includes the manufacturer/distributor name.

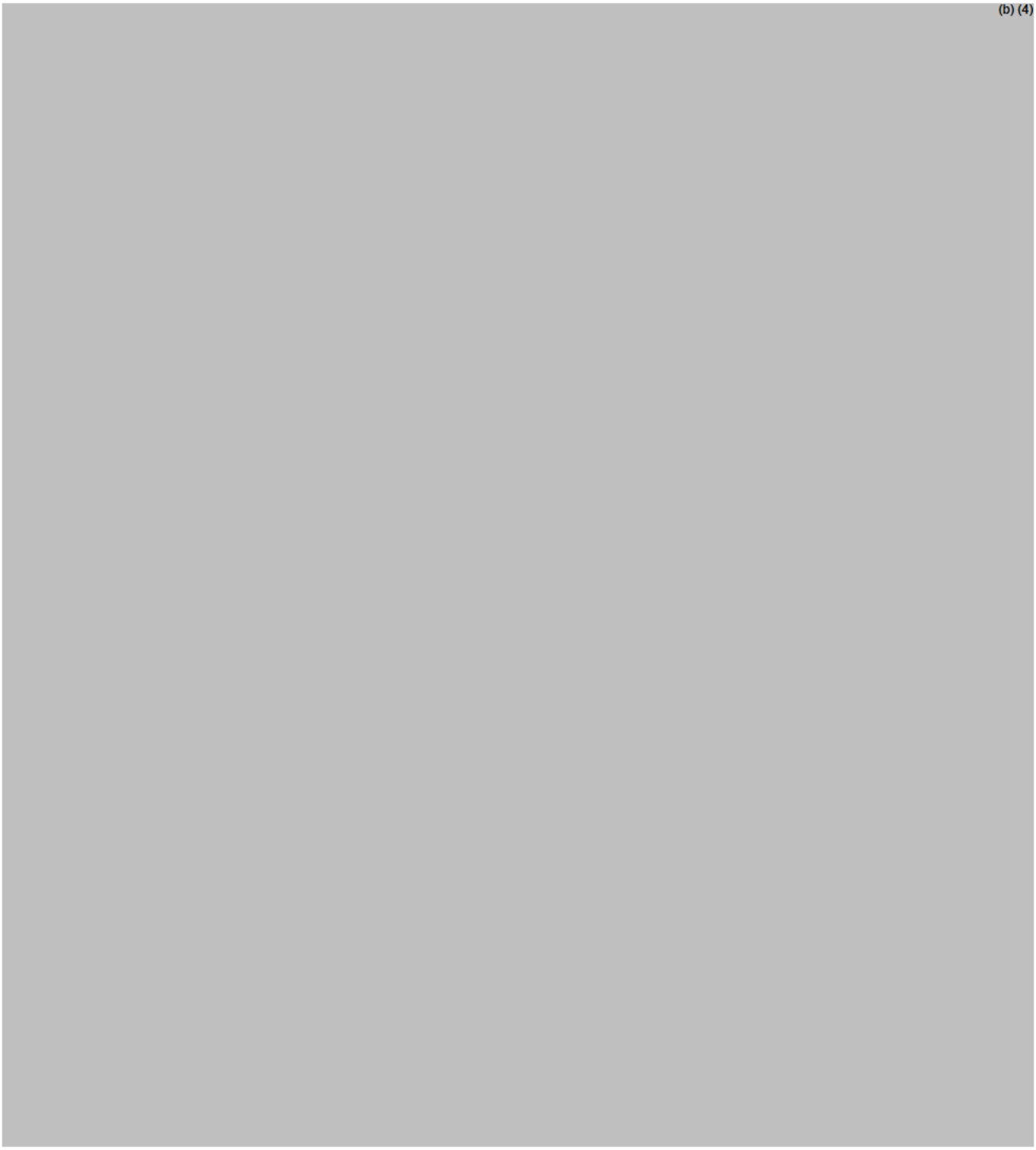
This section is **Unsatisfactory.**

2. Labels

1) Immediate Container Label

As of 3/8/2016 eCTD (0022)

(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))	RELISTOR® (methylnaltrexone bromide)	**Satisfactory.**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Each tablet contains: Methylnaltrexone, 122.5 mg (equivalent to 150 mg Methylnaltrexone Bromide)	**Satisfactory.**
Net contents (21 CFR 201.51(a))	6 Tablets 60 Tablets 90 Tablets	**Satisfactory.**
Lot number per 21 CFR 201.18	Displayed	**Satisfactory.**
Expiration date per 21 CFR 201.17	Displayed	**Satisfactory.**
"Rx only" statement per 21 CFR 201.100(b)(1)	Displayed	**Satisfactory.**
Storage (not required)	Displayed	**Satisfactory.**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed Not displayed on the Physician sample	**Satisfactory.**
Bar Code per 21 CFR 201.25(c)(2)**	Displayed	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
Others		

*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:

1. The description of the identifying characteristics of the tablet dosage and strength are adequately expressed.

2. The strength of the tablet includes an equivalency statement.
3. Net content, lot number, expiration date, manufacturer, and storage conditions are clearly displayed.
4. NDC number and Bar code are adequately displayed on the 60 and 90 tablet containers but not the physician sample. NDC number for the 6 tablet physician sample is displayed on the Carton.

This section is **Satisfactory.**

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))	RELISTOR® (methylnaltrexone bromide) tablets	**Satisfactory.**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Each tablet contains: Methylnaltrexone, 122.5 mg (equivalent to 150 mg Methylnaltrexone Bromide).	**Satisfactory.**
Net contents (21 CFR 201.51(a))	Displayed	**Satisfactory.**
Lot number per 21 CFR 201.18	Displayed	**Satisfactory.**
Expiration date per 21 CFR 201.17	Displayed	**Satisfactory.**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Not Displayed	**Satisfactory.**
Sterility Information (if applicable)	Not applicable	**Satisfactory.**
"Rx only" statement per 21 CFR 201.100(b)(1)	Displayed	**Satisfactory.**
Storage Conditions	Displayed	**Satisfactory.**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	**Satisfactory.**
Bar Code per 21 CFR 201.25(c)(2)**	Displayed (only space is designated)	**Satisfactory.**
Name of manufacturer/distributor	Displayed	**Satisfactory.**
"See package insert for dosage information" (21 CFR 201.55)	Displayed	**Satisfactory.**
"Keep out of reach of children" (optional for Rx, required for OTC)	Not Displayed	**Satisfactory.**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Not Displayed	**Satisfactory.**

Conclusion:

1- **Carton is only used for the 6 tablet physician sample.**

2- **Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) includes an equivalency statement.**

This section is **Satisfactory.**

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The PI and labels have adequate information from the CMC perspective, except for the expression of strength. The strength (150mg) is expressed based on the active ingredient, methylnaltrexone bromide, and an equivalency statement should be included in the labeling as well as labels to comply with CDER salt policy.

Information Request (IR) was conveyed to the applicant via an email from the Office of Pharmaceutical Quality (OPQ) on March 3, 2016 requesting an inclusion of an equivalency statement for the labels of Immediate Container and Carton, and in response, the applicant submitted revised labels on March 8, 2016, and they are deemed Adequate.

Now, all the labeling and labels are satisfactory from the CMC perspective.

Sarah, Ibrahim, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

Sarah Ibrahim -S
Digitally signed by Sarah Ibrahim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah Ibrahim -S, 0.9.2342.19200300.100.1.1=2001591303
Date: 2016.03.15 17:32:35 -04'00'

Secondary Review Comments and Concurrence:

I agree with Dr. Ibrahim's assessment and concur with her conclusion.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

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Date: 2016.03.15 17:39:32 -04'00'

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Evaluation**	**Risk Mitigation**	**Final Risk**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Considering the drug substance and drug product physico-chemical properties and proper controls in place, risk to the drug product (tablets) quality is considered to be low.	Assay and stability of the drug product is assured by properly designed formulation, validated assay and protective packaging.	L
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4) , this drug product is expected to be completely dissolved in the stomach and the solubility of the drug substance does not vary considerably across the physiological pH range of 1.2 to 7.2.	Through the established dissolution and particle size distribution (PSD) controls in place.	L
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4)	Through assurance of PSD control, adequate process parameters and process controls, and finished product testing, see pages 70-71 of this review.	L
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Finished product (b) (4) • Release/stability testing	L	(b) (4) The risk of microbial growth is low. Risk is low for solid dosage forms (tablets) for oral administration.	Finished product microbial testing and adequate (b) (4) control, and storage.	L
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipment • Site	M	Due to the drug substance's high solubility, the risk is low. However, since the DS permeability is low, the overall risk is moderate from the biopharmaceutics perspective.	(b) (4) Thus, the risk is mitigated via adequately designed formulation and properly validated dissolution method in place.	L