

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207621Orig1s000

CHEMISTRY REVIEW(S)

Review of Labeling Changes

NDA 207621
12/4/2015
Review #3

Drug Name/Dosage Form	Troxyca (Oxycodone HCl and Naltrexone HCl)/Capsules
Strength	10mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer Inc.
US agent, if applicable	N/A

On 9/14/2015, CMC recommended approval of Troxyca ER (Oxycodone HCl/Naltrexone HCl) 10mg/1.2mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60mg/7.2mg, 80mg/9.6mg capsules pending the overall recommendation from the drug product group and the Office of Compliance.

The drug product group recommendation is pending the resolution for the following deficiencies:

1. (b) (4) in the release specification for the drug Product
2. Clarification if the analytical methods have been validated for the registration batches

The drug product deficiencies have been resolved. The Office of Compliance has given an acceptable overall recommendation for the facilities.

Conclusion: Based on the recommendation from the following disciplines, drug substance, process, microbiology, drug product, biopharmaceutics, and facilities, CMC recommends the approval of Troxyca ER (Oxycodone HCl/Naltrexone HCl) 10mg/1.2mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60mg/7.2mg, 80mg/9.6mg capsules.



CHEMISTRY REVIEW TEMPLATE



Review of Labeling Changes

ADMINISTRATIVE

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.
Application Technical Lead
Quality Assessment Lead (Acting)
CDER/OPQ/ONDP/DIVII/Branch IV

Review of Labeling Changes

NDA 207621
Review #2

Drug Name/Dosage Form	Troxyca (Oxycodone HCl and Naltrexone HCl)/Capsules
Strength	10mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer Inc.
US agent, if applicable	N/A

An IR was sent to the applicant on 10/15/2015

(b) (4)

The applicant changes the wording as follows (New label shown below):

*Start of Sponsor Material.***Old text:**

(b) (4)

New text: Dispense in tight (USP), light-resistant, child-resistant containers.*End of Sponsor Material.***Evaluation:** Adequate. The sponsor has agreed

(b) (4)



CHEMISTRY REVIEW TEMPLATE



Review of Labeling Changes

ADMINISTRATIVE

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.
Application Technical Lead
Quality Assessment Lead (Acting)
CDER/OPQ/ONDP/DIVII/Branch IV



QUALITY ASSESSMENT



Recommendation: Pending

NDA 207621

Review #1

9/14/2015

Drug Name/Dosage Form	Troxyca (Oxycodone HCl and Naltrexone HCl)/Capsules
Strength	10mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	SUBMISSION DATE
Original Submission	12-DEC-2014
Response to Quality Information Request	20-FEB-2015
Response to CMC Information Requested	07-APR-2015
Response to CMC Information Requested	04-MAY-2015
Response to CMC Information Requested	11-MAY-2015
Response to CMC Information Requested	5-JUN-2015
Response to Quality Information Request	24-JUN-2015
Response to CMC Information Requested	14-JUL-2015
Response to CMC Information Requested	03-AUG-2015
Response to CMC Information Requested	06-AUG-2015
Response to CMC Information Requested	12-AUG-2015
Response to Quality Information Request	17-AUG-2015
Response to Quality Information Request	24-AUG-2015
Response to CMC Information Requested	07-APR-2015
Response to CMC Information Requested	04-SEP-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Benjamin Stevens, Ph.D.	II/New Drug API
Abuse Deterrence Category 1	Benjamin Stevens, Ph.D.	II/New Drug API
Drug Product	Venkateswara Pavuluri, Ph.D.	II/Drug Product
Process	Yong Hu, Ph.D.	DPAII/Branch VI
Microbiology	Yong Hu, Ph.D.	OPF/DMA
Facility	Sunita Lyer	DIA/ Branch III
Biopharmaceutics	Tien Mien Chen, Ph.D.	DB/Branch III
Project/Business Process Manager	Steven Kinsley, Ph.D.	OPRO/IO



CHEMISTRY REVIEW



Application	Technical Lead	Ciby Abraham, Ph.D.	DNP II/Branch IV
Laboratory (OTR)		N/A	
ORA Lead		Paul Perdue	ORA/OO
<u>Environmental Assessment</u> (EA)		N/A	

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QUALITY ASSESSMENT



Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	5/26/2015	
	Type II			Adequate	4/20/2015	
	Type IV			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	
	Type III			Adequate	N/A	



QUALITY ASSESSMENT



(b) (4) Type III			
Type V	(b) (4)	Adequate	N/A
		Adequate	N/A

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107037	
IND	(b) (4)	

3. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendation from the following disciplines, drug substance, process, microbiology, and biopharmaceutics, CMC recommends the approval of Troxyca ER (Oxycodone HCl/Naltrexone HCl) 10mg/1.2mg, 20mg/2.4mg, 30mg/3.6mg, 40mg/4.8mg, 60mg/7.2mg, 80mg/9.6mg capsules pending the overall recommendation from the drug product group and the Office of Compliance.

The drug product group recommendation is pending the resolution for the following deficiencies:

1. [REDACTED] ^{(b) (4)} in the release specification for the drug product
2. Clarification if the analytical methods have been validated for the registration batches

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Product

Drug Substance

The drug substance, Naltrexone HCl is manufactured [REDACTED] ^{(b) (4)} and is referenced in DMF# [REDACTED] ^{(b) (4)} (adequate, last reviewed 5/26/2015). Naltrexone Hydrochloride is a white to slightly off-white powder [REDACTED] ^{(b) (4)}. The retest period for naltrexone HCl is [REDACTED] ^{(b) (4)} months, when stored [REDACTED] ^{(b) (4)}.

The drug substance, Oxycodone HCl is manufactured [REDACTED] ^{(b) (4)} and is referenced in DMF# [REDACTED] ^{(b) (4)} (adequate, last reviewed 4/20/2015). Oxycodone Hydrochloride is a white or



QUALITY ASSESSMENT



almost white powder [REDACTED] (b) (4)
oxycodone HCl is [REDACTED] (b) (4) months, when stored [REDACTED]

The retest period for
(b) (4)

Drug Product

Troxyc ER capsules are provided in 6 strengths, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg of oxycodone HCl/naltrexone HCl for oral administration. All strengths are [REDACTED] (b) (4) encapsulated in hard gelatin capsule shells. A 36 month expiry is granted for each strength of the Troxyc ER capsules, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg with a storage statement of 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F). The sponsor claims that their product has abuse deterrent properties. For example, if the capsule is crushed the sequestered naltrexone HCl will be released (opioid antagonist) and offset the euphoric affects of the oxycodone HCl. A summary of the Category 1 studies can be found on page 11.

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

Troxyc (Oxycodone HCl and Naltrexone HCl) is intended to be used as an extended-release opioid analgesic for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, and biopharmaceutics pending the overall recommendation from the drug product group and the Office of Compliance.



QUALITY ASSESSMENT



Executive Risk Assessment Summary

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	<ul style="list-style-type: none">• Formulation• Raw materials• Process parameters• Scale/equipment• Site	L	-	N/A	-
Physical stability (API)	<ul style="list-style-type: none">• Formulation• Raw materials• Process parameters• Scale/equipment• Site	L	-	N/A	-
Content uniformity	<ul style="list-style-type: none">• Formulation• Raw materials• Process parameters• Scale/equipment• Site	H	(b) (4)	Acceptable	-
Microbial Limits	<ul style="list-style-type: none">• Formulation• Raw materials• Process parameters• Scale/equipment	L	-	N/A	-
Alcohol Dose Dumping	<ul style="list-style-type: none">• Formulation• Raw materials	H	-	Acceptable	There is no dose dumping detected in the in vitro dose



QUALITY ASSESSMENT



	<ul style="list-style-type: none">• Process parameters• Scale/equipment• Site• Exclude major reformulations<ul style="list-style-type: none">• Alcohol dose dumping			dumping study under the condition tested.
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*Risk ranking applies to product attribute/CQA

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



I. Administrative

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.

Quality Assessment Lead (Acting)

Application Technical Lead

ONDP/DIVII/Branch IV

Overview of In Vitro Studies

Troxyca ER is a proposed abuse deterrent extended release oxycodone drug product for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (see Figure 1 below). The product is available in 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg (oxycodone HCl/naltrexone HCl) strengths. The abuse deterrence mechanism relies on the incorporation of naltrexone, a μ -opioid receptor antagonist, into the drug product pellets. The naltrexone antagonist is sequestered from the oxycodone agonist by a membrane [REDACTED] (b) (4)

[REDACTED] This membrane acts as a barrier for naltrexone release in aqueous solutions, but can be disrupted by certain organic solvents or physical manipulations (*i.e.*, crushing, grinding). Therefore, such manipulations ideally result in an inseparable mixture of the two drug substances in sufficient concentrations to effectively limit the euphoric and analgesic effects of the agonist. [REDACTED] (b) (4)

Troxyca ER formulation technology does not limit tampering of the outer capsule. It is noted that the applicant incorrectly states [REDACTED] (b) (4)

[REDACTED] **It is unclear how pervasive this mischaracterization is throughout the remaining sections of the application as filed. The CSS group was notified of this issue (communication of 10-APR-2015).** [REDACTED] (b) (4)

(b) (4)

Figure 1. ALO-02 (Troxyc ER) Pellet Schematic Diagram

See Table 1 for the studies included under the *in vitro* abuse deterrent section of the application.

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ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:

The applicant proposes to exclude microbial limits in the drug product specification.

A microbial limits test was developed and validated for ALO-02 capsules. All clinical batches were tested for microbial quality at release and were found to contain no more than (b) (4) counts (bacteria), not more than (b) (4) counts (molds and yeasts) and an absence of E. coli per (b) (4) g. Microbial limits testing has been performed for the registration stability batches yearly throughout the three year registration stability program and were found to contain no more than (b) (4) counts (bacteria), not more than (b) (4) counts (molds and yeasts).

Based on no observable microbial growth at either time of release or on stability, and from an evaluation of ICH Q6A Decision Tree #8, a microbial limit test has not been included on the drug product specification.

In addition, the final manufacturing process for ALO-02 pellets is (b) (4)

Reviewer's Assessment: Adequate.

This reviewer concurs with the exclusion of microbial limits in the drug product specification (b) (4)

2.3.P.6 Reference Standards or Materials

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

Reviewer's Assessment: Not applicable.

This is not a sterile product.

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

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

Applicant's Response:

(b) (4)

The applicant has provided

(b) (4)

Reviewer's Assessment: Adequate.

The information provided is adequate.

(b) (4)

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

Not applicable.

Reviewer's Assessment: Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Acceptable.

Supervisor Comments and Concurrence: Signed for Dr. Zhigang Sun

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE BIOPHARMACEUTICS

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

The Biopharmaceutics review is focused on the evaluation of the dissolution method development report to support the proposed method and acceptance criteria, biowaiver request with supportive dissolution profile data, the in vitro alcohol dose-dumping study, and the in vitro stability/compatibility study when the capsule content is sprinkled on applesauce for patients who could not swallow capsules.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERIA

The proposed dissolution method and its acceptance criteria for Oxycodone and Naltrexone are shown below:

Table 1. The Conditions and Acceptance Criteria for the Dissolution of Oxycodone from Troxyca Capsules

Apparatus	II (Paddles)
Media	1 hour in 0.1 N HCl (aq) followed by 23 hours in 0.05 M phosphate buffer, pH 6.0
Volume	500 mL
Temperature	37 ± 0.5°C
Agitation rate	75 rpm
Capsules per vessel	1 (for all strengths)
Specification Acceptance Criteria	1 Hour NMT ^(b) (4)% 10 Hour ^(b) (4)% 24 Hour NLT ^(b) (4)%

Table 2. The Conditions and Acceptance Criteria for the Sequestering Limit of Naltrexone from ALO-02 Capsules

Apparatus	II (Paddles)
Media	1 hour in 0.1 N HCl (aq) followed by 72 hours in 0.05 M phosphate buffer, pH 7.5
Volume	500 mL
Temperature	37 ± 0.5°C
Agitation rate	100 rpm
Capsules per vessel	Oxycodone HCl/Naltrexone HCl 10 mg/1.2 mg: 12 20 mg/2.4 mg: 6 30 mg/3.6 mg: 4 40 mg/4.8 mg: 3 60 mg/7.2 mg: 2 80 mg/9.6 mg: 2
Specification Acceptance Criteria	73 Hour NMT ^(b) (4)% (b) (4)

Reviewer's Assessment:

The analytical method validation reports for Oxycodone and Naltrexone are reviewed and found acceptable.

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

Troxyca is formulated as ALO-02 pellets contained in a hard gelatin capsule for oral administration at 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg oxycodone HCl/naltrexone HCl, respectively. (b) (4)

The clinically tested formulation is the TBM (to-be-marketed) formulation.

Table 10. Compositions of Pilot Oxycodone HCl and Sequestered Naltrexone HCl Capsules and the ALO-02 Capsules used in Clinical Studies, and the Proposed Commercial Formulation

	Pilot Formulations (mg/capsule)	Phase 3/Proposed Commercial Formulation ^a (mg/capsule)					
		10 mg/1.2 mg	20 mg/2.4 mg	30 mg/3.6 mg	40 mg/4.8 mg	60 mg/7.2 mg	80 mg/9.6 mg
Strength	(b) (4)	D1100296 ^b	D1100297 ^b	D1100298 ^b	D1100299 ^b	D1100300 ^b	D1100301 ^b
Formulae Identifier		D1100307 ^b	D1100309 ^b	D1100310 ^b	D1100311 ^b	D1100312 ^b	D1100313 ^b
Oxycodone HCl		D1400179 ^c	D1400258 ^c	D1400181 ^c	D1400182 ^c	D1400183 ^c	D1400184 ^c
Naltrexone HCl							(b) (4)
Talc							
Ammonio methacrylate copolymer							
Sugar spheres	(b) (4)						
Ethylcellulose	(b) (4)						
Hydroxypropyl cellulose	(b) (4)						
Polyethylene glycol	(b) (4)						
Dibutyl sebacate							
Sodium lauryl sulfate							
Diethyl phthalate							
Magnesium stearate							
Methacrylic acid copolymer							
Ascorbic acid							
Hard gelatin capsule							
Strength	(b) (4)	10 mg/1.2 mg	20 mg/2.4 mg	30 mg/3.6 mg	40 mg/4.8 mg	60 mg/7.2 mg	80 mg/9.6 mg
Theoretical capsule fill weight	(b) (4)	D1100296 ^b	D1100297 ^b	D1100298 ^b	D1100299 ^b	D1100300 ^b	D1100301 ^b

- a. Phase 3 blinded clinical capsules - (b) (4) opaque capsules
 b. Phase 3 unblinded clinical capsules - strength differentiated by size and color
 c. Commercial capsules - strength differentiated by size, color and printing
 d. (b) (4)

(b) (4)

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Reviewer's Assessment:

The following provide evidences to support the adequacy of the proposed formulation:

1. The clinically tested formulation is the TBM (to-be-marketed) formulation.

(b) (4)

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Appendix 1

Summary of Formulation Employed in the Clinical Studies

The formulations evaluated during the development of ALO-02 drug product are summarized in [Table 3.2.P.2.2-1](#) along with the clinical studies and study numbers.



(b) (4)

The proposed commercial ALO-02 pellet formulation (No. D1200001) was used in several Phase 1 and all Phase 3 clinical studies (b) (4)

Appendix 2

Individual and Mean Dissolution Data (n=12 capsules/batch) for All Six Strengths

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OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:**Reviewer's Overall Comment**

From the Biopharmaceutics Perspectives, 1). The dissolution method development report and the proposed dissolution method and acceptance criteria, 2). Biowaiver request with supporting comparative dissolution profile data, 3). In vitro stability/compatibility of capsule contents sprinkling on applesauce, 4) *In Vitro* alcohol dose-dumping study, and 5). *In Vitro* stability of sprinkiling the capsule contents on applesauce submitted to this NDA have been reviewed by Division of Biopharmaceutics and found acceptable.

Therefore, this NDA is acceptable to support the proposed Troxyca ER capsules of six strengths.

Supervisor Comments and Concurrence:

Concur.

John Z. Duan

Note: additional reviewers can be added, as appropriate

(b) (4)

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

Labeling & Package Insert

The name of the drug product as listed in the labeling is **TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules, for oral use, CII**

1. Package Insert

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

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: TROXYCA ER extended release capsules Established Name: Oxycodone	Acceptable from CMC perspective

Item	Information Provided in NDA	Reviewer's Assessment
	hydrochloride and Naltrexone hydrochloride extended-release capsules	
Dosage form, route of administration	Dosage: Capsules Route: Oral	
Controlled drug substance symbol (if applicable)	CII	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended-release capsules (oxycodone hydrochloride/naltrexone hydrochloride): 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg	

Conclusion: Acceptable from CMC perspective.

(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Capsules	Adequate
Strengths: in metric system	10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	See Table below for Description of all six dosage strengths.	

TROXYCA ER is available in 6 strengths as extended-release hard gelatin capsule filled with common pellets as noted below:

Strength (oxycodone hydrochloride/naltrexone hydrochloride)	Description
10 mg/1.2 mg	Hard gelatin capsule, silver opaque body with "NTO 10" printed in black ink, yellow opaque cap with "Pfizer" printed in black ink
20 mg/2.4 mg	Hard gelatin capsule, silver opaque body with "NTO 20" printed in black ink, violet opaque cap with "Pfizer" printed in white ink
30 mg/3.6 mg	Hard gelatin capsule, silver opaque body with "NTO 30" printed in black ink, fuchsia opaque cap with "Pfizer" printed in black ink
40 mg/4.8 mg	Hard gelatin capsule, silver opaque body with "NTO 40" printed in black ink, olive green opaque cap with "Pfizer" printed in black ink
60 mg/7.2 mg	Hard gelatin capsule, silver opaque body with "NTO 60" printed in black ink, green opaque cap with "Pfizer" printed in black ink
80 mg/9.6 mg	Hard gelatin capsule, silver opaque body with "NTO 80" printed in black ink, brick red opaque cap with "Pfizer" printed in black ink

Conclusion: Acceptable

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

TROXYCA ER extended-release capsule contains pellets of oxycodone HCl with naltrexone HCl at a ratio of 100:12 in each capsule strength for oral administration. The capsule strength describes the amount of oxycodone HCl/naltrexone HCl per capsule. Oxycodone HCl is an agonist and naltrexone HCl is an antagonist at the mu-opioid receptor.

TROXYCA ER extended-release capsule contains the following inactive ingredients common to all strengths: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, hydroxypropyl cellulose, polyethylene glycol, dibutyl sebacate, sodium lauryl sulfate, diethyl phthalate, magnesium stearate, methacrylic acid copolymer, and ascorbic acid. Each TROXYCA ER capsule (as component of the capsule shell) also contains gelatin, titanium dioxide, E172 Black Iron Oxide, E172 Yellow Iron Oxide, and black ink.

The 10 mg/1.2 mg capsule does not contain additional excipient other than those listed above.
The 20 mg/2.4 mg capsule also contains FD&C Red #3, FD&C Blue #1, white ink.

The 30 mg/3.6 mg capsule also contains FD&C Blue #1, FD&C Red #3.

The 40 mg/4.8 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.

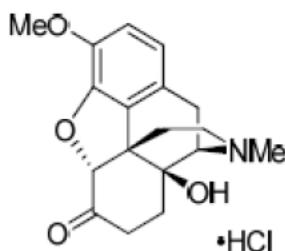
The 60 mg/7.2 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.

The 80 mg/9.6 mg capsule also contains FD&C Blue #1, FD&C Red #3, FD&C Yellow #6.

Oxycodone Hydrochloride

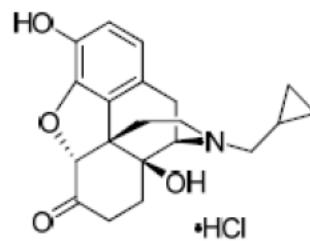
The chemical name of oxycodone HCl is 4,5 α -epoxy-14-hydroxy-3-methoxymorphinan-6-one hydrochloride. The empirical formula is C₁₈H₂₁NO₄•HCl and its molecular weight is 351.82.

Oxycodone HCl is white to off-white, fine powder. It has a solubility of 0.20 g/mL at pH 6. Its structural formula is:

**Naltrexone Hydrochloride**

The chemical name of naltrexone HCl is (5 α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride. The empirical formula is C₂₀H₂₃NO₄•HCl and its molecular weight is 377.86.

Naltrexone HCl is a white to slightly off-white powder that is soluble in water. Its structural formula is:



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TROXYCA ER extended-release capsule	Adequate
Dosage form and route of administration	Capsule, Oral	
Active moiety expression of strength with equivalence statement for salt (if applicable)	Oxycodone HCl with Naltrexone HCl at a ratio of 100:12 in each capsule strength.	
Inactive ingredient information (quantitative, if injectable 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Common to all strengths: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, hydroxypropyl cellulose, polyethylene glycol, dibutyl sebacate, sodium lauryl sulfate, diethyl phthalate, magnesium stearate, methacrylic acid copolymer, and ascorbic acid. Each TROXYCA ER capsule (as component of the capsule shell) also contains gelatin, titanium dioxide, E172 Black Iron Oxide, E172 Yellow Iron Oxide, and black ink. See below for additional components of the capsule shells of individual strengths.	
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	Oxycodone HCl is an agonist and naltrexone HCl is an antagonist at the mu-opioid receptor.	
Chemical name, structural formula, molecular weight	Oxycodone HCl: 4,5 α -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride, C18H21NO4•HCl, 351.82 Naltrexone HCl: (5 α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride, C20H23NO4•HCl, 377.86	
If radioactive, statement of important nuclear characteristics.	Not Applicable	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Oxycodone has a solubility of 0.20 g/mL at pH 6. Naltrexone is soluble in water.	

The 10 mg/1.2 mg capsule does not contain additional excipient other than those listed above.
The 20 mg/2.4 mg capsule also contains FD&C Red #3, FD&C Blue #1, white ink.

The 30 mg/3.6 mg capsule also contains FD&C Blue #1, FD&C Red #3.
The 40 mg/4.8 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.
The 60 mg/7.2 mg capsule also contains FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #6.
The 80 mg/9.6 mg capsule also contains FD&C Blue #1, FD&C Red #3, FD&C Yellow #6.

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

Oxycodone HCl / naltrexone HCl	TROXYCA ER 10 mg/1.2 mg	TROXYCA ER 20 mg/2.4 mg	TROXYCA ER 30 mg/3.6 mg	TROXYCA ER 40 mg/4.8 mg	TROXYCA ER 60 mg/7.2 mg	TROXYCA ER 80 mg/9.6 mg
Extended-Release Capsule Description	Two-toned hard gelatin capsule, silver opaque body, yellow opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, violet opaque cap, black print on body and white print on cap	Two-toned hard gelatin capsule, silver opaque body, fuchsia opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, olive green opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, green opaque cap, black print	Two-toned hard gelatin capsule, silver opaque body, brick red opaque cap, black print
NDC #	60793-537-01	60793-531-01	60793-535-01	60793-532-01	60793-533-01	60793-536-01

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Multiple Strengths, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg	Adequate
Available units (e.g., bottles of 100 Tablets)	Bottle count for each of these strengths is 100.	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See Table above for description and NDC numbers of all strengths	
Special handling (e.g., protect from light, do not freeze)	None	
Storage conditions	Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).	

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)	Distributed by Pfizer Inc. New York, NY 10017	Adequate

Overall Conclusion for package insert: The information contained in sections 3, 11, and 16 of package insert meets the CFR 201.57 requirements

2. Labels

1) Immediate Container Label

Representative Container Labels for 10 mg/1.2 mg and 80 mg/9.6 mg are reproduced below.

(b) (4)



Reviewer's Assessment: Adequate. Container labels for all six strengths are similar in layout, except for the dosage strength designation. The dosage strength text is printed in white color and six strengths are differentiated by background color scheme. The three lower dosage strengths 10 mg/1.2 mg, 20 mg/2.4 mg and 40 mg/4.8 mg having similar text while the two higher strengths, 60 mg/7.2 mg and 80 mg/9.6 mg have additional text designating them “For use in opioid-tolerant patients only” printed in white, against red color background.

The label text include NDC number, proprietary name and established names for the two active ingredients, dosage form type and strength, Controlled Substance designation, dispensing (in child proof, light resistant (b) (4) container) and storage instructions, and name of the distributor.

Conclusion: Acceptable. The labels have all required information from CMC perspective.

Cartons: Not applicable (No Carton label or text included in the submission).

II. List of Deficiencies Communicated to Applicant

Drug Product:

1. Provide a [REDACTED] ^{(b) (4)} limit for total degradation products of Oxycodone Hydrochloride [REDACTED] ^{(b) (4)} of NMT [REDACTED] ^{(b) (4)} %.
2. Provide rationale for the selection of [REDACTED] ^{(b) (4)} studies for quantities of ascorbic acid (^{(b) (4)} % w/w of naltrexone HCl) used in ALO-02 pellets, either by way of referencing [REDACTED] ^{(b) (4)} or by providing other data not already included in the NDA.
3. Provide copies of relevant chromatograms obtained from analysis of the samples after forced degradation studies and standard solutions of the drugs [REDACTED] ^{(b) (4)} for both oxycodone and naltrexone, marking individual peaks with their RT values.
4. Explain the [REDACTED] ^{(b) (4)} attachment (file name- 2015 08 QQ1 NDA 207621 July 29, 2015) in response to information request, email of 8/4/2015.
5. [REDACTED] ^{(b) (4)} for naltrexone HCl assay in Table 3.2.P.3.4-1 [REDACTED]
6. The justification provided [REDACTED] ^{(b) (4)} is not acceptable. [REDACTED] ^{(b) (4)}
7. [REDACTED] ^{(b) (4)}

Provide information [REDACTED] ^{(b) (4)} and how they were standardized.
8. [REDACTED] ^{(b) (4)}

III. Attachments

- A. Lifecycle Knowledge Management - Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking *	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Release and Stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale / equipment • Site 	Release - L Stability - L	(b) (4)	Low at Release and Stability	The drug product has a 3 year proposed shelf life at 25°C. (b) (4)
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale / equipment • Site 	L	(b) (4)	Low	Oxycodone HCl is stable at (b) (4) °C (b) (4) Naltrexone HCl is stable for (b) (4) months, when stored (b) (4)
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale / equipment • Site 	M	(b) (4)	Low, Acceptable	Assay ratio of Oxycodone HCl and Naltrexone HCl (b) (4) in pellets (b) (4)

*Risk ranking applies to product attribute/CQA

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



QUALITY REVIEW



IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: **Venkateswara R. Pavuluri**, 9/9/2015

Secondary Reviewer Name/Date: **Julia. C. Pinto**,

Project Manager Name/Date:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207621 **Submission Type:** NDA 505b(2)

Established/Proper Name:
Troxycodone ER (Oxycodone HCl and Naltrexone HCl)

Applicant: Pfizer Inc.

Letter Date: 12/19/2014

Dosage Form: Capsules

Chemical Type: Non-NME

Stamp Date: 12/19/2014

Strength: 10mg, 20mg, 30mg, 40mg, 60mg, and 80mg

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	x		CMC: Yes Biopharmaceutics: Yes
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		x	

B. NOTEWORTHY ELEMENTS OF THE APPLICATION			Yes	No	Comment
Product Type					
1.	New Molecular Entity ¹	<input type="checkbox"/>	x		
2.	Botanical ¹	<input type="checkbox"/>	x		
3.	Naturally-derived Product	<input type="checkbox"/>	x		
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	x		
5.	PET Drug	<input type="checkbox"/>	x		
6.	PEPFAR Drug	<input type="checkbox"/>	x		
7.	Sterile Drug Product	<input type="checkbox"/>	x		
8.	Transdermal ¹	<input type="checkbox"/>	x		
9.	Pediatric form/dose ¹	<input type="checkbox"/>	x		
10.	Locally acting drug ¹	<input type="checkbox"/>	x		
11.	Lyophilized product ¹	<input type="checkbox"/>	x		
12.	First generic ¹	<input type="checkbox"/>	x		
13.	Solid dispersion product ¹	<input type="checkbox"/>	x		
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	x		
15.	Modified release product ¹	x			Extended release of Oxycocne HCl
16.	Liposome product ¹	<input type="checkbox"/>	x		
17.	Biosimilar product ¹	<input type="checkbox"/>	x		

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B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
18.	Combination Product _____	X		Contains Oxycodone HCl and Naltrexone HCl
19.	Other _____	<input type="checkbox"/>	X	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	x	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	x	<input type="checkbox"/>	Agreements met
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	x	
24.	Comparability Protocol(s) ²	x	<input type="checkbox"/>	
25.	Other _____ Abuse Deterrent Properties _____	x	<input type="checkbox"/>	The sponsor is claiming that their product has abuse deterrent properties. If the capsule is crushed the sequestered Naltrexone HCl will be released (opioid antagonist) and offset the euphoric affects of the Oxycodone HCl.
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	x	
27.	Design Space	<input type="checkbox"/>	x	
28.		<input type="checkbox"/>	x	
29.		<input type="checkbox"/>	x	
30.		<input type="checkbox"/>	x	
31.		<input type="checkbox"/>	x	
32.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	x	
33.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	x	
34.	Alternative Microbiological Test Methods	<input type="checkbox"/>	x	
35.	Process Analytical Technology ¹	<input type="checkbox"/>	x	
36.	Non-compendial Analytical Procedures and/or specifications	<input type="checkbox"/>	x	
37.		<input type="checkbox"/>	x	
38.		<input type="checkbox"/>	x	
39.	Unique analytical methodology ¹	<input type="checkbox"/>	x	(b) (4)
40.	Excipients of Human or Animal Origin	x		
41.	Novel Excipients	<input type="checkbox"/>	x	
42.	Nanomaterials ¹	<input type="checkbox"/>	x	
43.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	x	
44.	Genotoxic Impurities or Structural Alerts	x		(b) (4)
45.	Continuous Manufacturing	<input type="checkbox"/>	x	
46.	Other unique manufacturing process ¹	<input type="checkbox"/>	x	
47.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input type="checkbox"/>	
48.	New delivery system or dosage form ¹	<input type="checkbox"/>	x	
49.	Novel BE study designs	<input type="checkbox"/>	<input type="checkbox"/>	
50.	New product design ¹	<input type="checkbox"/>	x	
	Other	<input type="checkbox"/>	x	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION					

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FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> <input type="radio"/> Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) <input type="radio"/> Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only <input type="radio"/> Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="radio"/> Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) <input type="radio"/> Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="radio"/> Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 	x	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> <input type="radio"/> Includes descriptions of changes in the manufacturing process from material used 	x	<input type="checkbox"/>	<input type="checkbox"/>	

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C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> in clinical to commercial production lots <ul style="list-style-type: none"> Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) Includes data to demonstrate process consistency (i.e. data on process validation lots) Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) Analytical validation package for release test procedures, including dissolution <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	<p>Does the application contain dissolution data?</p> <ul style="list-style-type: none"> Is the dissolution test part of the DP specifications? Does the application contain the dissolution method development report including data supporting the discriminating ability? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
9.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> Does the application contain the complete BA/BE data? 	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Clinpharm will review the BA/BE studies.

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C. FILING CONSIDERATIONS				
<ul style="list-style-type: none"> • Are the PK files in the correct format? <p>Is an inspection request needed for the BE study(ies) and complete clinical site information provided?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10. Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Biopharm reviewer will check the in vitro data and Clinpharm reviewer will check with in vivo data.
11. Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12. For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
13. For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The Applicant did not request.
REGIONAL INFORMATION AND APPENDICES				
14. Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15. Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16. Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="radio"/> manufacturing flow; adjacent areas <input type="radio"/> other products in facility <input type="radio"/> equipment dedication, preparation, sterilization and storage <input type="radio"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="radio"/> avoidance and control procedures <input type="radio"/> cell line qualification <input type="radio"/> other materials of biological origin <input type="radio"/> viral testing of unprocessed bulk <input type="radio"/> viral clearance studies <input type="radio"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17. Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example:			<input checked="" type="checkbox"/>	

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C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ LAL instead of rabbit pyrogen ○ Mycoplasma <p>Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples</p>				

Risk Assessment

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMEA RPN Number	Comment
Assay, stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 					(b) (4) The drug product has a 3 year proposed shelf life at 25 °C. (b) (4)
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 					Oxycodone HCl is stable at (b) (4) °C (b) (4) Naltrexone HCl is stable (b) (4) when stored (b) (4)
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 					(b) (4)
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters 					(b) (4)

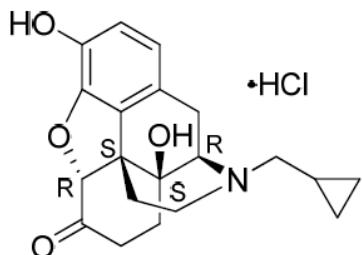
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	<ul style="list-style-type: none"> • Scale/equipment • Site 	(b) (4)	
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping 	(b) (4)	Potential alcohol dose dumping - opioid

CMC:

Drug Substance

Naltrexone



Molecular Formula

HCl Salt: C₂₀H₂₄ClNO₄

Free Base: C₂₀H₂₃NO₄

Molecular Weight

HCl Salt: 377.86 Daltons

Free Base: 341.40 Daltons

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FILING REVIEW

Impurities

Name	Chemical Name	Structure	Source (b) (4)

Name	Chemical Name	Structure	Source (b) (4)

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FILING REVIEW

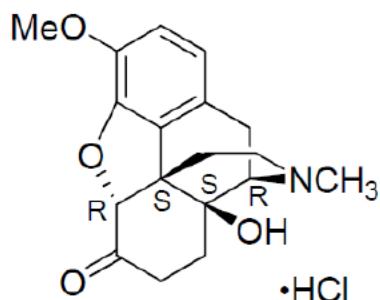
<u>Test</u>	<u>Specification</u>	<u>Result</u>
Appearance	White to off-white, (b) (4) powder	Pass
Identity	(b) (4)	
Melting Range: Starting Point		
Melting Range: End Point		
Melting Range		
IR	Matches IR of USP Oxycodone Standard	Pass
Specific Rotation	(b) (4)	
Residue on Ignition	(b) (4)	
Chromatographic Purity	(b) (4)	(b) (4)
Chromatographic Purity (HPLC)	(b) (4)	
Assay by HPLC		
Oxycodone Hydrochloride	(b) (4)	

The drug substance Naltrexone HCl is manufactured (b) (4). Full details of the sysnthesis and manufacturing process can be found in DMF (b) (4), which was last reviewed in 2/5/2013 and was found adequate. There is a discrepancy for the specifications of naltrexone and the speicifactions shown in the certificate of analysis. (b) (4)

(b) (4)

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FILING REVIEW

Oxycodone HCl



Molecular Formula

(b) (4)

Hydrochloride salt: C₁₈H₂₂ClNO₄ (anhydrous)

Free base: C₁₈H₂₁NO₄

Molecular Weight

(b) (4)

Hydrochloride salt: 351.82 Daltons (anhydrous)

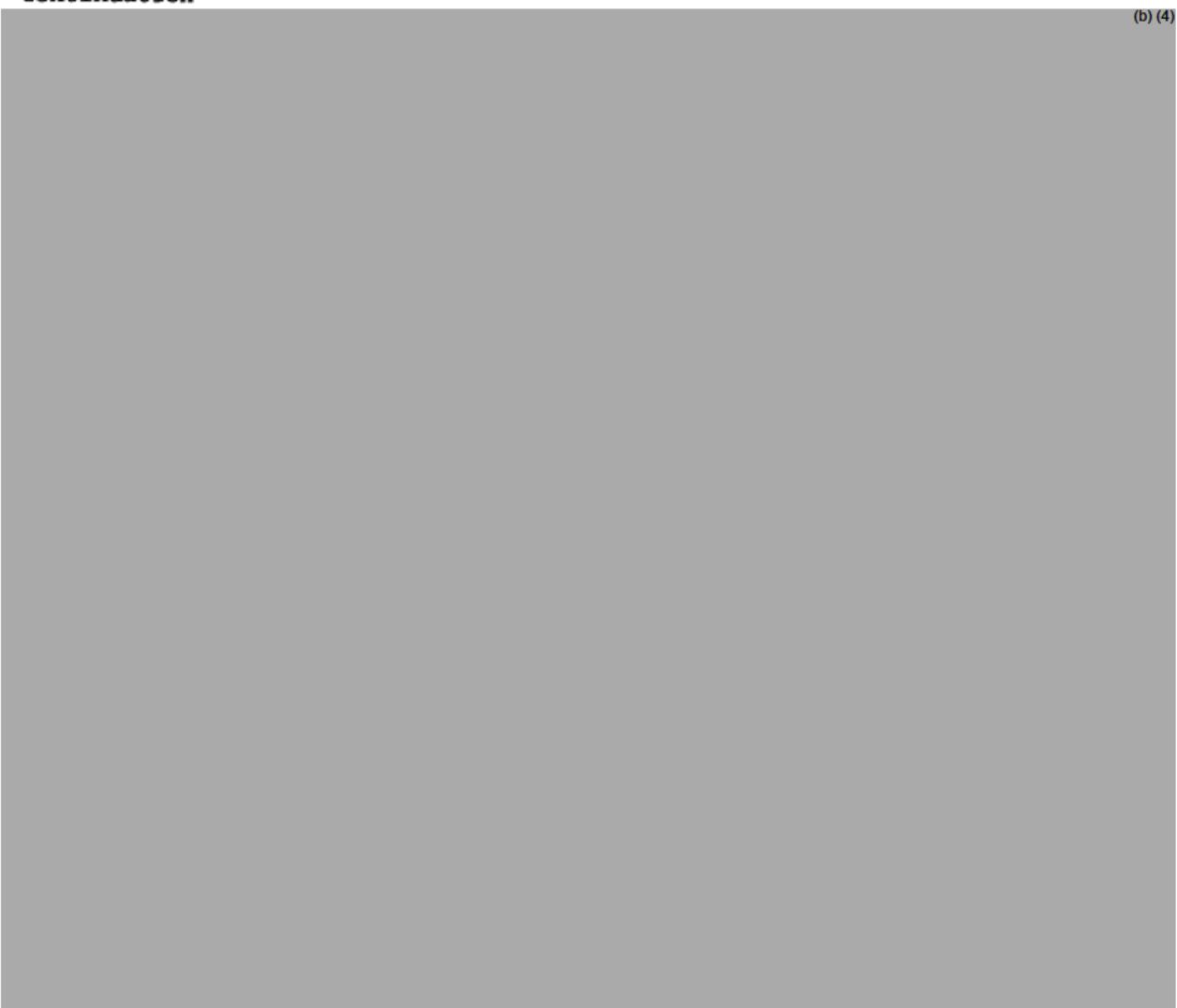
Free base: 315.36 Daltons

TESTS	LIMITS	RESULTS
APPEARANCE	WHITE TO SLIGHTLY OFF-WHITE POWDER	WHITE POWDER
COMPLETENESS OF SOLUTION (USP<641>)	CLEAR SOLUTION	CLEAR SOLUTION
IDENTIFICATION (IR) (USP<197K>)	MATCHES REFERENCE STANDARD	MATCHES REFERENCE STANDARD
SPECIFIC ROTATION (b) (4)	(b) (4)	(b) (4)
RESIDUE ON IGNITION (USP<281>)		
HEAVY METALS (USP<231> (b) (4))		
LIMIT OF TOTAL SOLVENTS (USP) (b) (4)		

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FILING REVIEW

Continuation

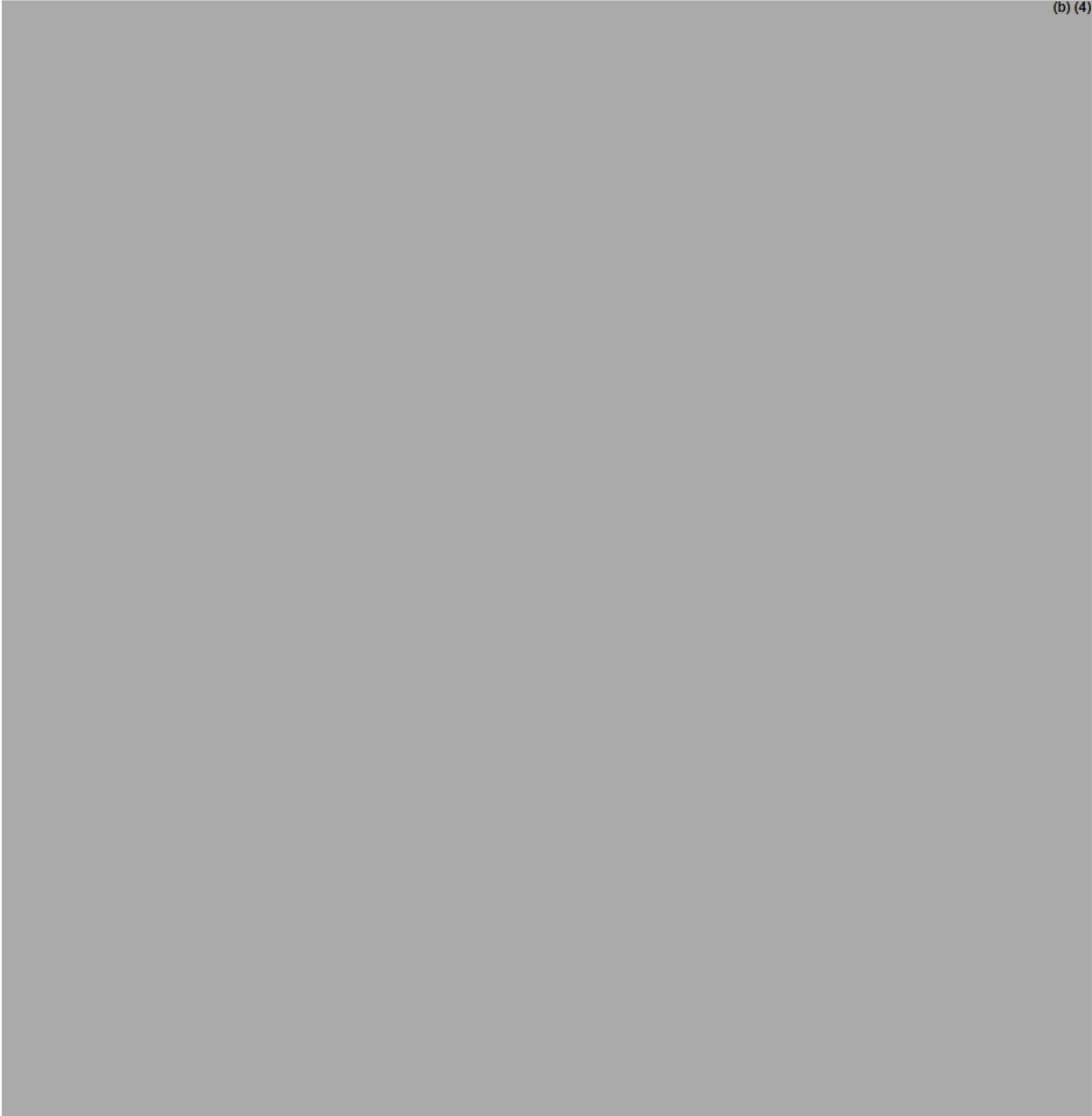
(b) (4)



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(b) (4)



The drug substance Oxycodone HCl is manufactured [REDACTED] ^{(b) (4)}. Full details of the sysnthesis and manufacturing process can be found in DMF [REDACTED] ^{(b) (4)} which was last reviewed in 7/23/2014 and was found adequate. The shelf life and retest period for Oxycodone HCl is [REDACTED] ^{(b) (4)}

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Facilities

Drug Subsance

Table 3.2.S.2.1-1. Site and Responsibilities for Manufacture and Testing of Naltrexone Hydrochloride

Site	Responsibility
(b) (4)	Manufacture Testing

Table 3.2.S.2.1-1. Sites and Responsibilities for Manufacture and Testing of Oxycodone HCl

Site	Responsibility
(b) (4)	Manufacturing Testing
(b) (4)	Manufacturing Testing
(b) (4)	

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Drug Product

Table 3.2.P.3.1-1. Sites and Responsibilities for ALO-02 Capsules

Site	Responsibility
(b) (4)	Manufacturing Testing
(b) (4)	Packaging and Labeling
(b) (4)	Stability Testing

Process

The commercial ALO-02 capsule strengths of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg oxycodone HCl/naltrexone HCl are manufactured

(b) (4)

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Components

Manufacturing Step

(b) (4)

(b) (4)

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Drug Product

Troxyca ER Capsules are provided in 6 strengths, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg of oxycodone HCl/naltrexone HCl for oral administration. All strengths are [REDACTED] (b) (4) encapsulated in hard gelatin capsule shells. The packaging information is shown below. Details are described in 3.2.P.7 Container Closure System - HDPE Bottles. All excipients are compendial grade. The ink and color used are made compendial ingredients. [REDACTED] (b) (4)

[REDACTED] Stability: 36 month proposed expiration 25°C (77°F) with excursions permitted to 15°C -30°C (59°F-86°F). [REDACTED] (b) (4)

Table 3.2.P.7.1-1. Packaging Systems, Commercial Product Launch

HDPE Bottle/Closure System			
Strength (mg/mg) Oxycodone HCl/Naltrexone HCl	Count	Bottle Size (cc)	Closure Size (mm)
10/1.2	100	[REDACTED] (b) (4)	
20/2.4	100		
30/3.6	100		
40/4.8	100		
60/7.2	100		
80/9.6	100		

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Table 3.2.P.1-1. Theoretical Composition of ALO-02 10 mg/1.2 mg Capsules

	Reference to Standard	Function(s)	Unit Formula ^a			
			Unit (mg)	%		
Pellet Composition						
Active Components:						
Oxycodone HCl	In house	Active	10.00	(b) (4)		
Naltrexone HCl	In house	Active	1.20			
Inactive Components:						
Talc	USP/NF			(b) (4)		
Ammonio methacrylate copolymer (b) (4)	USP/NF					
Sugar spheres (b) (4)	USP/NF					
Ethylcellulose (b) (4)	USP/NF					
Hydroxypropyl cellulose (b) (4)	USP/NF					
Polyethylene glycol (b) (4)	USP/NF					
Dibutyl sebacate	USP/NF					
Diethyl phthalate	USP/NF					
Sodium lauryl sulfate	USP/NF					
Methacrylic acid copolymer (b) (4) (b) (4)	USP/NF					
Magnesium stearate	USP/NF					
Ascorbic acid (b) (4)	USP/NF					
	In house					
	USP/NF					
	USP/NF					
	USP/NF					
Target Capsule Fill Weight	--					

Hard Gelatin Capsule Shell			
Capsule shells (size # (b) (4)silver opaque/yellow opaque)	In house	Encapsulation	1 capsule (b) (4)
Black iron oxide (E172)	USP/NF		
Yellow iron oxide (E172)	USP/NF		
Titanium dioxide	USP/NF		
Gelatin	USP/NF (b) (4)		
Approximate weight of capsule shell	--		
Print Ink^g			
Approximate weight of print ink on capsule shell	--		

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Table 3.2.P.5.1-1. ALO-02 Capsule Specification

Test	Analytical Procedure Number	Acceptance Criteria
Physical Characteristics		
Description (Visual)	TM-01-1923A	Capsule appearance is appropriate to the strength under test, as designated in Table 3.2.P.5.1-2. Each capsule contains (b) (4) (b) (4) pellets.
Identification¹		
Identity (HPLC)	TM-01-1919A	The retention times of the oxycodone and naltrexone peaks in the assay preparation correspond to the retention times of the oxycodone and naltrexone peaks in the standard preparation.
Identity (TLC)	TM-01-1918A	The Rf values of oxycodone and naltrexone spots in the sample solution are comparable to the Rf value of the oxycodone and naltrexone spots from the standard solution and spots should be similar in shape and size.
Assay		
Oxycodone HCl Assay (HPLC)	TM-01-1919A	(b) (4)
Naltrexone HCl Assay as % of Oxycodone HCl assay (HPLC)	TM-01-1919A	
Degradation Products (HPLC)		
Oxycodone HCl Specified Impurity:	TM-01-1920A (b) (4)	
Individual Unspecified impurities Total Degradation Products		
Naltrexone HCl Specified Impurity:	TM-01-1920A (b) (4)	
Individual Unspecified impurities Total Degradation Products		

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Table 3.2.P.5.4.3-1 Batch Analysis Results for the Primary Stability Batches

	(b) (4)
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Table 3.2.P.5.1-1. ALO-02 capsule specification (continued)

Test	Analytical Procedure Number	Acceptance Criteria
Performance		
Dissolution of Oxycodone HCl	TM-01-1921A	<u>Time</u> 1 hour NMT (b) (4)% dissolved 10 hours (b) (4)% dissolved 24 hours NLT (b) (4)% dissolved
Sequestering Limit of Naltrexone HCl	TM-01-1922A	<u>Time</u> 73 Hours NMT (b) (4)% released for each vessel
(b) (4)		
Uniformity of Dosage Units¹		
Oxycodone HCl Content Uniformity (HPLC)	TM-01-1919A USP <905>	Meets requirements of USP <905> Acceptance Value NMT (b) (4)
Naltrexone HCl Content Uniformity (HPLC)	TM-01-1919A USP <905>	Meets requirements of USP <905> Acceptance Value NMT (b) (4)

¹ Tested at release only

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Review Issues Identified:

- *None.*

BIOPHARMACEUTICS ASSESSMENT

SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission: It is fileable from the Biopharm perspective.

- The proposed dissolution method and acceptance criteria for both Oxycodone and Naltrexone are submitted as shown below.

Table 2.3.P.2-9. Dissolution Conditions and Acceptance Criteria for the Dissolution of Oxycodone from ALO-02 Capsules

Apparatus	II (Paddles)
Media	1 hour in 0.1 N HCl (aq) followed by 23 hours in 0.05 M phosphate buffer, pH 6.0
Volume	500 mL
Temperature	37 ± 0.5°C
Agitation rate	75 rpm
Capsules per vessel	1 (for all strengths)
Specification Acceptance Criteria	1 Hour NMT (4) ^(b) % 10 Hour (b)(4)% 24 Hour NLT (4)%

Table 2.3.P.2-10. Dissolution Conditions and Acceptance Criteria for the Sequestering Limit of Naltrexone from ALO-02 Capsules

Apparatus	II (Paddles)
Media	1 hour in 0.1 N HCl (aq) followed by 72 hours in 0.05 M phosphate buffer, pH 7.5
Volume	500 mL
Temperature	37 ± 0.5°C
Agitation rate	100 rpm
Capsules per vessel	Oxycodone HCl/Naltrexone HCl 10 mg/1.2 mg: 12 20 mg/2.4 mg: 6 30 mg/3.6 mg: 4 40 mg/4.8 mg: 3 60 mg/7.2 mg: 2 80 mg/9.6 mg: 2
Specification Acceptance Criteria	73 Hour NMT (4) ^(b) % (b)(4)

- The biowaiver request was submitted under M1.12.5. The comparative *in-vitro* oxycodone dissolution data with the f2 calculations and the *in-vitro* naltrexone sequestering data are detailed in technical report INX 100186300 titled "ALO-02 Capsules Comparative

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Oxycodone Hydrochloride Dissolution Profiles and Sequestering Limits of Naltrexone Hydrochloride.”

- Analytical procedures for both Oxycodone and Naltrexone are submitted under M32P52.
- *In Vitro* Alcohol dose-dumping study was conducted and submitted for review: Comparative dissolution studies have been performed to evaluate the impact of 5% to 40% ethanol (aqueous) on the *in-vitro* release of both oxycodone HCl and naltrexone HCl from the proposed commercial ALO-02 formulations on: 1). 20 mg/2.4 mg ALO-02 Capsules - The capsule strength used in clinical study B4531004 and 2). 80 mg/9.6 mg ALO-02 Capsules – The highest strength capsule. Note: A clinical Study B4531004 was conducted to evaluate the effects *in vivo* of administration of ALO-02 with 20% or 40% ethanol on oxycodone pharmacokinetics. The issues had been discussed in the IND meetings.
- The OCP (Office of Clinical Pharmacology) will review the *in vivo* PK studies.

Review Issues Identified: None at this time!

Biopharmaceutics Comments for 74-Day Letter: None at this time!

CMC Comments for 74-Day Letter: No Comments from CMC.

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