CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

CHEMISTRY REVIEW(S)

CMC Memo To File

Date	June 25 2014
NDA	205777
Sponsor:	Purdue Pharma
Drug:	Targiniq ER Tablets
CMC Lead	Julia Pinto, Ph.D.
Acting BC	Eric Duffy, Ph.D.

The CMC NDA review (June 14, 2014, Jean Nashed, Ph.D.) states that sufficient CMC information is provided, to assure the identity, strength, purity, and quality of the drug product. However, because of an outstanding deficiency for DMF (b) (4), supporting the Naloxone HCl, active ingredient, this NDA was recommended as approvable pending resolution of the deficiency noted in the DMF review by the Office of Generic Drugs (DMF Review by Weiqin Jiang, Ph.D, OGD). The deficiency concerns the modification of the manufacturing process, (b) (4) Under GDUFA, the reviewer, recommended the processes be split into two DMFs. Therefore, since the deficiency is not safety or quality related, and since sufficient data is provided within the NDA to support the Naloxone Drug Substance obtained from (b) (4) under this DMF, NDA 205777 is recommended for approval from the CMC perspective.

Further, during the CMD review of the NDA, the Maximum Daily Dose (MDD) had not yet been established by the Firm and agreed upon by the Clinical team. The drug product release and stability specifications were set according to the ICH guidance based on an MDD of not more than 100mg of Oxycodone. An agreement was put in place with the firm to tighten the specifications, if the MDD was approved at higher than 100mg (J. Nashed, CMC Review #1).
Currently, the Clinical Team has determined the MDD to be 80mg/40mg (Oxycodone/Naloxone). The drug product release and stability specifications as illustrated in the NDA are therefore supported by ICH Q3B for an MDD of less than 100mg and by the batch and stability data submitted in the NDA.

Julia Pinto, Ph.D.
CMC Lead, Branch VIII

Eric Duffy Ph.D.
Acting Branch Chief/ Director
ONDQA BranchVIII

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/s/

JULIA C PINTO
06/27/2014

ERIC P DUFFY
07/07/2014

NDA 205-777

Targiniq (oxycodone hydrochloride and naloxone hydrochloride) Extended Release Tablets, 10/5mg, 20/10mg and 40/20mg

PurduePharma, L.P.

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III

for

Division of Anesthesia, Analgesia, and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 205-777

2. REVIEW NUMBER: 1

3. REVIEW DATE: June 12, 2014

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSIONS BEING REVIEWED (Chem. Rev #1):

Submission(s) Reviewed	Document Date
Original	September 23, 2013
Amendement	October 31, 2013
Amendment	December 9, 2013
Amendment	December 24, 2013
Amendment	January 22, 2014
Amendment	March 24, 2014
Amendment	April 10, 2014
Amendment	April 30, 2014

7. NAME AND ADDRESS OF APPLICANT:

Name: PurduePharma, L.P. (Purdue Fredrick Co.)
Address: 1 Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901-3431
Tel.: 203-588-8000

8. Product Drug Code and Name:
a) Proprietary Name: Targiniq
b) Non-Proprietary Name (USAN): Oxycodone Hydrochloride and Naloxone Hydrochloride Extended Release Tablets
c) Code name/#(ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only): 4 S (New combination)

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: Combination of Opioid Agonist (oxycodone) and Opioid Antagonist (naloxone)

11. DOSAGE FORM: Extended Release Tablets (film-coated, capsule shaped)

12. STRENGTH/POTENCY: 10mg/5mg (white), 20mg/10mg (pink), and 40mg/20mg (yellow)

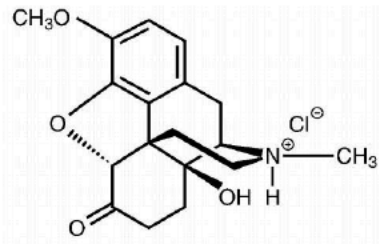
13. ROUTE OF ADMINSITRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

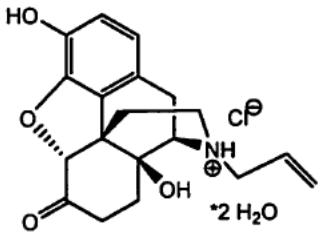
__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{18}H_{21}NO_4$•HCl MW 351.83

Oxycodone Hydrochloride
USAN name: Oxycodone HCl, USP
IUPAC name:
4,5(alpha)-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride



C $H_{21}NO_4$ • HCl • $2H_2O$ M.W. 399.87

Naloxone Hydrochloride (b) (4)
Chemical Name: (5R,9R,13S,14S)-17-Allyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one hydrochloride (b) (4)
CAS number: [51481-60-8]

Chemistry Review Data Sheet

17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	Type	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE Review Completed	COMMENTS
(b) (4)	2		(b) (4)	3	Adequate	08-15-13 09-07-10	(b) (4)
	2			3	INADEQUATE	06-03-14 (OGD)	
	2			3	Adequate	05-21-14	
	4			4	Adequate	05-30-14	
	3			4	Adequate	09-10-12	
	5			4	Adequate	10-04-13	
	3			4	Adequate	07-22-13	
	3			4	Adequate	01-31-12	
	3			4	Adequate	11-09-12	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,851	Oxycodone HCl/Naloxone HCl ER Tablets
NDA (cross-referenced)	20-553	Oxycontin
NDA (cross-referenced)	22-272	Reformulated Oxycontin

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	Acceptable	Jan 2014	Steven Donald, Ph.D.
EES	Current overall OC recommendation is AC, as of April 24, 2014	Apr 2014	Office of Compliance;
Pharm/Tox	Pending		Belinda Hayes, Ph.D.
Biopharm	Pending		Kareen Riviere, Ph.D.
LNC	NA		
Methods Validation	NA		Standard analytical methodology; Request for validation is not planned
DMET/DDMAC	Acceptable	Dec 2013	Name acceptable; labeling pending
EA	Categorical exclusion satisfactory	Oct 2013	Refer to p. 65 of this review

The Chemistry Review for NDA 205777

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is approvable from the CMC perspective providing that the Applicant addresses satisfactorily the remaining CMC deficiency (i.e., inadequate DMF (b) (4) for drug substance naloxone hydrochloride) and an Acceptable recommendation is maintained by the Office of Compliance (OC). The current EER recommendation from the OC is ACCPTABLE, as of April 24, 2014, based on record review. Refer to the Summary Report on page 61 of this review.

The above approvable recommendation is based on the assumption that the maximum total daily dose (MTDD) is below 100 mg (80 mg/40 mg of oxycodone hydrochloride/naloxone hydrochloride claimed by the Applicant). However, data supporting this claim have not been submitted yet and the review of the incoming amendment(s) may require reassessment of the overall CMC recommendation. A separate amendment to this review will be filed to address the pending submissions concerning the MTDD and any status changes (currently deficient) for DMF (b) (4)

Overall, the current recommendation from the CMC team is the Complete Response action due to insufficient supporting documentation for drug substance, i.e., deficient DMF (b) (4) for naloxone hydrochloride. Advisory letter informing of the inadequate status for supporting DMF (b) (4) was forwarded to the Applicant on June 4, 2014.

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

The following comments are based on the Agreements submitted by the Applicant in amendment dated April 30, 2014:

1. We remind you of the agreement provided in NDA amendment dated April 30, 2014, to work with drug substance supplier(s) to tighten the proposed acceptance criteria for individual impurities (e.g., (b) (4) to the ICH Q3A–recommended levels. Submit revised acceptance specifications for drug substances and provide a table listing maximum daily intake for each impurity and total impurities, based on the proposed acceptance criteria and documented maximum daily dose. Include references to the nonclinical qualification studies as needed.

2. We remind you of the agreement provided in NDA amendment dated April 30, 2014, to re-evaluate the currently proposed acceptance criteria for individual and total impurities based on the reassessed Maximum Target Daily Dose (MTDD), and modify the criteria to reflect

the data and comply with ICH Q3B – recommended thresholds. We request that you submit one specification sheet for each strength of the drug product, specifying differences between the release and stability testing attributes, methods and acceptance criteria, as needed.

3. We remind you of the agreement provided in NDA amendment dated April 30, 2014, to submit statistical evaluation of the stability data for drug product supporting the proposed acceptance criteria and the requested expiry period. Discuss observed instability trends and provide graphic comparison of impurity profiles for drug product batches manufactured with naloxone HCl obtained from (b) (4) (old process), (b) (4) (new process) and from (b) (4). Clearly identify which batches are the most representative of the to-be-marketed product (the same formulation, manufacturing, container closure and tablet count) and focus your analysis and proposed acceptance criteria on these batches.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

Targiniq (oxycodone hydrochloride/naloxone hydrochloride) extended-release tablets is a fixed-dose combination product of opioid agonist oxycodone and opioid antagonist naloxone. It is intended for twice-daily (every 12 hours) dosing for the indication of treatment of (b) (4) pain (b) (4) around the clock (b) (4). It has been developed by Purdue Pharma L.P., in dosage strengths of 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg, as an extended-release formulation. The presence of naloxone and the extended-release formulation matrix are intended as a remedy for drug abuse and the Applicant claims it to be an abuse-deterrent formulation. Similar/the same combination products of oxycodone hydrochloride and naloxone hydrochloride are approved for adults in the European Union, Canada, and Australia.

The drug product is manufactured by Purdue Pharma at Wilson, NC, at the scale ranging from (b) (4) (40 mg/20 mg strength) to (b) (4) tablets (10 mg/5 mg strength). The manufacturing process includes (b) (4) Each drug product tablet (b) (4) contains 2 parts oxycodone hydrochloride and 1 part naloxone hydrochloride (2:1 ratio) on an anhydrous, assay corrected, mg/mg basis. The formulation contains compendial excipients and include stearyl alcohol and Ethyl Cellulose (b) (4). The extended-release tablets are capsule-shaped, film coated and debossed with ONX on one side and oxycodone strength on the other. The tablets are color coded to distinguish different strengths with 10 mg/5 mg colored white, 20 mg/10 mg tablets colored pink, and 40 mg/20 mg tablets colored yellow.

Each drug product strength is supplied in opaque HDPE bottles of 100 tablets and has child-resistant closure. It has to be stored at 25°C (77°F), with excursions permitted between 15°-30°C (59°-86°F. It has to be protected from light.

The Sponsor is seeking an expiry period of 24 months for each drug product presentation. The provided stability data indicate that all batches are within the currently proposed specification limits. However, the currently proposed specifications were proposed based on MTDD of NMT (b) (4) which was not adequately assessed and justified by the Applicant. Possible future change of the MTDD may require changing of the acceptance criteria for impurities and reassessment of the data supporting the proposed expiry period. Refer to Agreements provided by the Applicant on April 30, 2014, regarding the drug product specifications and stability data, as listed on page 8 of this review (item #2 and #3).

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

Targiniq (oxycodone hydrochloride/naloxone hydrochloride) extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg, are intended for twice-daily (every 12 hours) dosing for the indication of treatment of (b) (4) pain (b) (4) around the clock (b) (4). The presence of naloxone and the extended-release formulation matrix are intended as a remedy for drug abuse and the Applicant claims it to be an abuse-deterrent formulation. Similar/the same combination products of oxycodone hydrochloride and naloxone hydrochloride are approved for adults in the European Union, Canada, and Australia.

C. Basis for Approvability Recommendation

The Complete Response recommendation by the CMC team is based on deficient DMF supporting the alternate source of drug substance. The complete list of CMC comments (hold and non-hold) for forwarding to the Applicant is provided at the end of this review. The major issues include the following:

- Deficient DMF (b) (4) supporting alternate source for naloxone hydrochloride.

  (b) (4) This NDA application can't be recommended for approval until all supporting DMFs have adequate review status. DMF Deficiency letter dated June 3, 2014, was sent to the DMF holder, and the Advisory letter dated June 4, 2014, was sent to the Applicant.

- Agreements provided by the Applicant in amendment dated April 30, 2014.

  The current acceptance criteria for impurities are based on the assumption of MTDD of NMT (b) (4). The Applicant is reassessing MTDD and plans additional data submission in this regard. The new MTDD will trigger a reassessment of acceptance criteria for impurities and reassessment of drug product expiry period. The following Agreements were proposed by the Applicant in amendment dated April 30, 2014:

- Agreed to work with drug substance supplier(s) to tighten the proposed acceptance criteria for individual impurities (e.g., (b) (4) to the ICH Q3A–recommended levels.

- Agreed to re-evaluate the currently proposed acceptance criteria for individual and total impurities based on the reassessed Maximum Target Daily Dose (MTDD), and modify the criteria to reflect the data and comply with ICH Q3B – recommended thresholds.

- Agreed to submit statistical evaluation of the stability data for drug product supporting the proposed acceptance criteria and the requested expiry period.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Eugenia Nashed, Ph.D.
CMC Lead: Julia Pinto, Ph.D.
Project Manager: Lisa Basham, M.S.
Division Director: Eric Duffy, Ph.D.

Office of New Drug Quality Assessment (ONDQA), Division III

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/s/

EUGENIA M NASHED
06/14/2014

JULIA C PINTO
06/18/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 205777

2. DATES AND GOALS:

Letter Date: September 16, 2013	Submission Received Date :
PDUFA Goal Date: July 23, 2014	September 23, 2013

3. PRODUCT PROPERTIES:

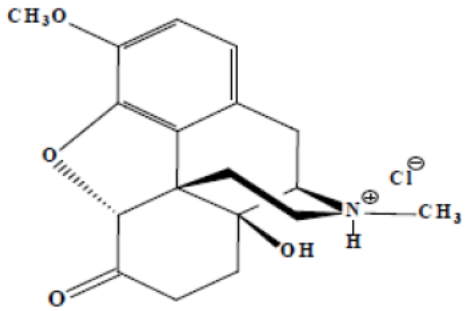
Trade or Proprietary Name:	Targiniq™
Established or Non-Proprietary Name (USAN):	Oxycodone HCl/Naloxone HCl Controlled-Release Tablets
Dosage Form:	Controlled Release Tablets
Route of Administration	Oral
Strength/Potency	10/5 mg; 20/10mg and 40/20mg
Rx/OTC Dispensed:	Rx

INDICATION:

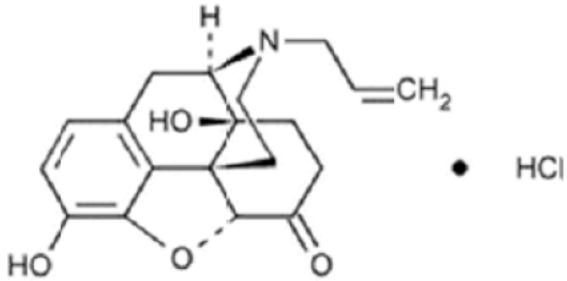
The management of (b) (4) pain (b) (4), around-the-clock (b) (4).

The Formulation is an abuse-deterrant formulation and granted Fast Track/Priority Review status.

4. DRUG SUBSTANCE STRUCTURAL FORMULA:



Oxycodone Hydrochloride



Naloxone Hydrochloride

5. NAME OF APPLICANT (as indicated on Form 356h):

Purdue Pharma L.P.
One Stamford Forum
201 Tresser Blvd
Stamford, CT 06901-3431

6. SUBMISSION PROPERTIES:

Review Priority:	Priority Review
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAAAP

7. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		EES entered September 26, 2013 by Luz Riviera
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology Consult Sent: September 30, 2013 Steven Donald is the assigned Microbiologist Reviewer

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes **X** No
CMC Filing Issues: **None**
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes X No
CMC Comments for 74-Day Letter:
1. Provide Certificates of Analysis from all Suppliers for all batches of drug substances used in Toxicology and Clinical batches of drug product. Provide a comparative table demonstrating which batches of drug substances correspond to which batches of drug product were used for toxicology, clinical and stability studies respectively. Provide corresponding Purdue batch numbers for each of the Supplier Batch numbers. 2. Release and Stability Testing of the Drug Product should include testing for Moisture Content per USP <921>.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes X No
Biopharmaceutics Filing Issues:
1. See Biopharmaceutics Filing Review at end of this Document

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
Biopharmaceutics Comments for 74-Day Letter:
1. See Biopharmaceutics Filing Review attached at the end of this Document.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes X No
Microbiology Filing Issues: None
See Microbiology Filing Review by Steven Donald for details and for any potential Microbiology review issues

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No X
Suggested expertise for team:		

Summary of Critical Issues and Complexities

Initial Quality Assessment

The drug product is a film coated, extended release tablet, manufactured using 2 active pharmaceutical ingredients, oxycodone hydrochloride USP and naloxone hydrochloride USP in a 2:1 ratio. The release mechanism of the controlled release tablets (b) (4) with stearyl alcohol and ethylcellulose (b) (4). The Tablet strengths are 10/5mg, 20/10mg and 40/20mg Oxycodone/Naloxone for twice daily dosing. A comparative composition is shown below

Table 2.3.P.1. Comparative Composition of Oxycodone HCl/Naloxone HCl q12h Tablets 10/5 mg, 20/10 mg and 40/20 mg

Component	mg/tablet			Function	Reference to Standard
	10/5 mg	20/10 mg	40/20 mg		
Active Ingredient					
Oxycodone hydrochloride anhydrous[1]	10.00	20.00	40.00	Active Ingredient	USP
(b) (4)					
Naloxone hydrochloride	5.45	10.90	21.80	Active Ingredient	USP
(b) (4)					
Excipients				(b) (4)	
Lactose Monohydrate[2]					NF
Stearyl Alcohol					NF
Ethyl Cellulose (b) (4)					NF
Povidone (b) (4)					USP
Talc					USP
Magnesium Stearate					NF
(b) (4)					
(Polyvinylalcohol partially hydrolised)				(b) (4)	USP
(Titanium dioxide (b) (4))					USP
(Macrogol (b) (4),					NF
(Talc)					USP
(Iron oxide red (b) (4))					NF
(Iron oxide yellow (b) (4))					NF
(b) (4)					
Total	127.27	142.17	284.34		
(b) (4)					

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	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? **This question is not applicable for synthesized API.**			NA

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		All facilities for DS and DP are listed at the end of the document, prior to the Biopharmaceutics IQA.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	Referenced to DMF (b) (4) (Oxycodone HCl) DMF (b) (4) and DMF (b) (4) (Naloxone HCl) There are two vendors for the Naloxone API
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4) (Oxycodone HCl) DMF (b) (4) and DMF (b) (4) (Naloxone HCl) There are two vendors for the Naloxone API
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?		x	Referenced to DMF (b) (4) (Oxycodone HCl) DMF (b) (4) and DMF (b) (4) (Naloxone HCl) There are two vendors for the Naloxone API
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (b) (4) (Oxycodone HCl) DMF (b) (4) and DMF (b) (4) (Naloxone HCl) There are two vendors for the Naloxone API
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
25.	Does the section contain controls of the final drug product?	X		Batch Analysis data is provided drug product batches used in clinical studies. However corresponding COAs for the drug substance batches from the DS suppliers have not been included. A comparative table of DS batches used in each of the DP toxicology and clinical batches is also not included.
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

Drug Product Comparative Composition across all three strengths:

Table 2.3.P.1. Comparative Composition of Oxycodone HCl/Naloxone HCl q12h Tablets 10/5 mg, 20/10 mg and 40/20 mg

Component	mg/tablet			Function	Reference to Standard
	10/5 mg	20/10 mg	40/20 mg		
Active Ingredient					
Oxycodone hydrochloride anhydrous[1]	10.00	20.00	40.00	Active Ingredient	USP
Naloxone hydrochloride	5.45	10.90	21.80	Active Ingredient	USP
Excipients					
Lactose Monohydrate[2]					NF
Stearyl Alcohol					NF
Ethyl Cellulose					NF
Povidone					USP
Talc					USP
Magnesium Stearate					NF
(Polyvinylalcohol partially hydrolised)					USP
(Titanium dioxide					USP
(Macrogol					NF
(Talc)					USP
(Iron oxide red					NF
(Iron oxide yellow					NF
Total	127.27	142.17	284.34		

Drug Product Release Specifications for the 10/5 mg strength is below. The specifications for the other two strengths are the same but for the assay values that will correspond with the amount in the tablet strength. Moisture content and tablet hardness/friability are not included in the release testing. Both should be monitored as part of the release testing of the drug product.

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Bulk Tablets

TEST	SPECIFICATION/LIMIT	METHOD NUMBER
		(b) (4)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?		x	

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		x	This is a tablet formulation. However a microbiology reviewer is assigned to review the manufacturing process and container closure system for microbiological integrity.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		LOAs for all pertinent DMFs are provided.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**

32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

Manufacturing Facilities for Drug Substance and Drug Product:

Establishment information for manufacturing packaging and control facilities is provided in the following table. Additionally, identification of the onsite contact person with contact information is included. Manufacturing is conducted in accordance with Good Manufacturing Practices. The facilities are ready for GMP inspection.

Facility Name and Address (DMF number if applicable)	Site Registration Number	Contact Information	Function											
			Item	Manufacturing API=Active Ingredient DP=Drug Product DP Pkg= DP Packaging			Analytical R=Release, S=Stability, M=Micro API=Active Ingredient DPC=Drug Product Component DP=Drug Product PM=Packaging Materials						
				API	DP	DP Pkg	API		DPC		DP		PM
							R	S	R	M	R	S	R
(b) (4)														
Purdue Pharmaceuticals L.P. 4701 Purdue Drive Wilson, NC 27893 USA	3002960808 FEI 132080875 DUNS	Name Title Phone Fax e-mail	(b) (4) Oxycodone HCl Naloxone HCl OXN Tablets		X	bottles	X X		X		X	X	X

356h-attach-facilities-establishment-info-oxn

1 of 2

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

Facility Name and Address (DMF number if applicable)	Site Registration Number	Contact Information	Function										
			Item	Manufacturing API=Active Ingredient DP=Drug Product DP Pkg= DP Packaging			Analytical R=Release, S=Stability, M=Micro API=Active Ingredient DPC=Drug Product Component DP=Drug Product PM=Packaging Materials						
				API	DP	DP Pkg	API		DPC		DP		PM
							R	S	R	M	R	S	R
(b) (4)													

X=Performs function
X^C=Performs function (compendial testing only)

Biopharmaceutics Filing Review

NDA Number	205-777
Submission Date	9/23/2013
Product name, generic name of the active	Targiniq (oxycodone HCl/naloxone HCl controlled release)
Dosage form and strength	CR Tablet; 10/5, 20/10, and 40/20 mg
Applicant	Purdue Pharma L.P.
Clinical Division	DAAAP
Indication	the management (b) (4) pain (b) (4) around-the-clock (b) (4)
Type of Submission	505(b)(2) New Drug Application
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?	x		
35.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criterion.
36.	Does the application contain the dissolution method development report?	x		
37.	Is there a validation package for the analytical method and dissolution methodology?	x		
38.	Does the application include a biowaiver request?		x	However, a biowaiver is needed to support the acceptability of manufacturing site change for 20/10 mg strength.
39.	Is there information provided to support the biowaiver request?		x	Not Applicable.
40.	Does the application include a IVIVC model?		x	However, this NDA does include an IVIVR model for the oxycodone component of the drug product.

41.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not Applicable.
42.	Is there information/data on in vitro alcohol dose dumping?	x		There are also abuse deterrent studies (in vitro) and will be reviewed by ONDQA/Biopharm.
43.	Is there any *in vivo* BE information in the submission?	x		Relative bioavailability study ONU1009, which compares each component of Targiniq (oxycodone and naloxone) to OxyContin (oxycodone) and Narcan (naloxone), and the BE study OXN1403 supporting the interchangeability of the three strengths will be evaluated by the OCP Reviewer. BE studies ONU1001 and ONU1002 supporting the Level (b)(4) manufacturing site change as well as BE study OXN1004 supporting production batch scale-up will be reviewed by ONDQA/ Biopharmaceutics.
44.	Is there a complete bio-analytical method development and validation report?	x		

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
45.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	Not Applicable.
47.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}
Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment
10/28/13
Date

{See appended electronic signature page}
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment
10/28/13
Date

INITIAL BIOPHARMACEUTICS ASSESSMENT

This 505(b)(2) NDA references the listed drug Narcan, naloxone hydrochloride (NDA 016636) and cross-references original OxyContin®, oxycodone hydrochloride (NDA 020553) and reformulated OxyContin®, oxycodone hydrochloride (NDA 022272). The Applicant has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Targiniq (oxycodone and naloxone) to approved products, OxyContin (oxycodone) and Narcan (naloxone, via an ANDA generic designated as the Reference Listed Drug for Narcan).

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criterion, information/data on alcohol dose dumping, data supporting the acceptability of the Level (b)(4) manufacturing site change for each strength, data supporting production batch scale-up for each strength, and data supporting the *in vitro in vivo* relationship (IVIVR) for the oxycodone component of the proposed drug product.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 mL	37 °C	SGF (pH 1.2) w/o enzyme

The proposed acceptance criteria for both oxycodone HCl and naloxone HCl are:

10 mg/5 mg Strength

Acceptance Criteria	
15 min:	(b)(4) %
2 hr:	%
10 hr:	NLT (b)(4) %

20 mg/10 mg Strength

Acceptance Criteria	
15 min:	(b)(4) %
2 hr:	%
10 hr:	NLT (b)(4) %

40 mg/20 mg Strength

Acceptance Criteria	
15 min:	(b)(4) %
2 hr:	%
10 hr:	NLT (b)(4) %

The Biopharmaceutics review will focus on the evaluation and acceptability of:

1) the proposed dissolution methodology,
2) the proposed dissolution acceptance criteria,
3) information/data on *in vitro* alcohol dose dumping,

4) information/data on abuse deterrent studies (in vitro)
5) the BE and dissolution data supporting the Level (b) (4) manufacturing site change,
6) the BE and dissolution supporting production batch scale-up, and
7) data supporting the IVIVR model for the oxycodone component of the proposed drug product.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 205-777 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
NAME : Julia Pinto, Ph.D.
CMC-Lead
Division III
Office of New Drug Quality Assessment

{See appended electronic signature page}
NAME: Kareen Rivieri
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
NAME: Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader or Designee
Office of New Drug Quality Assessment

{See appended electronic signature page}
NAME: Prasad Peri, Ph.D.
Branch Chief or Designee
Division III
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA C PINTO
11/18/2013

KAREEN RIVIERE
11/18/2013

TAPASH K GHOSH
11/19/2013

PRASAD PERI
11/20/2013
I concur