CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

CHEMISTRY REVIEW(S)

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18-FEB-2010

TO: N 22272 File for OxyContin® (oxycodone hydrochloride controlled-release) Tablets

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of CMC-related labeling in the 04-FEB-2010, amendment of N22272

BACKGROUND: The DAARP sent a complete response letter to the applicant of N22272 dated 30-DEC-2009. There were no remaining CMC-related issues that were to be addressed by the applicant and the CMC team had recommended in the fourth CMC review dated 23-JUL-2009, that the application be approved. The latest resubmission contains labeling and labels that are revised from those last reviewed by the CMC team in the third CMC review dated 28-APR-2009. The revisions to the labeling and labels is the subject of this fifth CMC review.

EVALUATION: The package insert (PI) that was included in the 04-FEB-2010, amendment includes some revisions relative to the labeling in the 27-MAR-2009, amendment, which was the subject of the third CMC review. Specifically, in all places in the new PI, with the exception of the Structured Product Labeling data table and the header on the first page, the dosage form descriptor is "controlled-release tablets." In the exceptions, it is listed as an "extended-release tablet." Recall that ONDQA recommended to the clinical division that the applicant be asked to change the dosage form descriptor to "extended-release tablets" to be consistent with current policy. The DAARP decided that this would not be requested of Purdue as it may lead to confusion when the product was approved as a replacement for the older approved OxyContin, which currently is described as a "controlled-release tablet."

In the current USP there is a monograph entitled "Oxycodone Extended-Release Tablets." Because of differences in the acceptance criteria for dissolution for Purdue's current reformulated OxyContin, this product would not be able to meet the acceptance criteria in the USP monograph. Specifically, the new formulations of OxyContin will meet the following dissolution acceptance criteria:

Drug released (%)

Time/strength (mg)	**10**	15	**20**	30	**40**	60	**80**
1 hour	(b) (4)						
4 hours							
12 hours							

These acceptance criteria are different from what is in the USP for the 10, 20, 40, and 80 mg strength of oxycodone extended-release tablets, i.e.,

FOR TABLETS LABELED TO CONTAIN 10 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 20 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 40 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

FOR TABLETS LABELED TO CONTAIN 80 MG:

Time (hours)	Amount dissolved
1	between (b) (4)
4	between (b) (4)
12	not less than (b) (4)

In general, it is seen that at both 1 and 4 hours, the target *in vitro* release for the Purdue 10, 20, 40, and 80 mg reformulated product is less than the target represented by the USP monograph. However, at 12 hours, all acceptance criteria require not less than (b) (4) release.

Since the applicant is not using the monograph name for their reformulated product, and the clinical division finds this to be acceptable, there is no requirement that the applicant state in the labels and labeling that the drug product does not meet the USP monograph for Oxycodone

Extended-Release Tablets. Nevertheless, they have added the following statement to the DESCRIPTION section:

(b) (4)

To be more precise, this statement should be revised to the following:

> 'OxyContin 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets, as described in this section are not tested according to and do not meet the "Oxycodone Hydrochloride Extended-Release Tablets" monograph in the USP.'

Alternatively, the applicant could just remove reference to the USP monograph for Oxycodone Hydrochloride Extended-Release Tablets altogether in the PI as the USP specifically states:

> "The identity of an official article, as expressed by its name, is established if it conforms in all respects to the requirements of its monograph and other relevant portions of the compendia. The FD&C Act stipulates that an article may differ in strength, quality, or purity and still have the same name if the difference is stated on the article's label. FDA requires that names for articles that are not official must be clearly distinguishing and differentiating from any name recognized in an official compendium. Official preparations (a drug product, a dietary supplement including nutritional supplements, or a finished device) may contain additional suitable ingredients. (See General Notices.)"

Comment: *Revise the DESCRIPTION section of the labeling to state that the new OxyContin formulations 'do not meet the "Oxycodone Hydrochloride Extended-Release Tablets" monograph in the USP."' Alternately, remove the statement completely as you are not using the name from the official monograph.*

Other changes to the PI include the description of the dosage form in the DOSAGE FORMS AND STRENGTHS section of the HIGHLIGHTS portion. In the previous version the tablets were described as (b) (4) whereas in the new version, the tablets are described as "controlled-release." This change is acceptable and complies with the regulation 21 CFR 201.57(a)(8). Likewise, in the full DOSAGE FORMS AND STRENGTHS section, the tablets are no longer described as (b) (4) but are characterized as "film-coated." This section is compliant with 21 CFR 201.57(c)(4).

The only significant non-editorial change made to the DESCRIPTION section is the removal of the following statement:

(b) (4)

In addition, as already mentioned, the section now includes a statement indicating that the drug product does not comply with the USP monograph (see comment to be forwarded to the applicant above). Overall, this section is compliant with the information required by 21 CFR 201.57(c)(12).

The only change that has been made to the HOW SUPPLIED/STORAGE AND HANDLING section is that the tablets are no longer described as (b) (4) The section still complies with 21 CFR 201.57(c)(17).

The amendment also provides updated mock-up bottle labels for each of the strengths. Relative to the last set of labels that were reviewed by the CMC team from the 27-MAR-2009, amendment, the new versions include the following message:

The last reviewed version of the bottle labels included a clear indication of where the product lot number and expiration date would appear. That is no longer clear on the current revised versions, as can be seen in the example of the 10 mg strength label reproduced below:

Comment: *For each strength of the drug product, revise and resubmit the mock-ups of the bottle labels such that it is clear where the lot number and expiration date will be located.* (b) (4)

The only other notable change is the removal of the pictures of the actual dosage forms that had appeared on earlier versions of the bottle labels. Such pictures are not required by 201.100(b).

RECOMMENDATION: The following comments should be forwarded to the applicant by the PM. If there are other labeling comments to be forwarded by other members of the review team, these may be included with those rather than being sent under separate cover.

1. Revise the DESCRIPTION section of the labeling to state that the new OxyContin formulations 'do not meet the "Oxycodone Hydrochloride Extended-Release Tablets" monograph in the USP."' Alternately, remove the statement completely as you are not using the name from the official monograph.

2. For each strength of the drug product, revise and resubmit the mock-ups of the bottle labels such that it is clear where the lot number and expiration date will be located. (b) (4)

_____
Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-272
C.Bertha/ONDQA//Reviewer/2/18/10
PPeri/ONDQA/Acting Branch Chief_____
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	ORIG-1	PURDUE PHARMA INC	OXYCONTIN

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

/s/

CRAIG M BERTHA
02/19/2010

PRASAD PERI
02/19/2010
I concur

CHEMISTRY REVIEW

NDA 22-272

OxyContin® (oxycodone hydrochloride controlled-release) Tablets

Purdue Pharma L.P.

Craig M. Bertha, Ph.D.
ONDQA/Division I/Branch 2

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

Chemistry Review Data Sheet

1. NDA 22-272

2. REVIEW #: 4

3. REVIEW DATE: 20-JUL-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-NOV-2007 (assigned 17-DEC-2007)
Amendment (stability update)	18-DEC-2008 (assigned 24-DEC-2007)
Amendment (stability update)	15-FEB-2008 (assigned 15-FEB-2008)
Amendment (response to 74-day letter)	06-MAR-2008 (assigned 10-MAR-2008)
Amendment (individual dissolution data)*	07-MAR-2008 (assigned 10-MAR-2008)
Amendment (response to 13-FEB-2008 CMC DR)	13-MAR-2008 (assigned 17-MAR-2008)
Amendment (response to 05-MAR-2008 IR)*	17-MAR-2008 (assigned 19-MAR-2008)
Amendment (response to CMC IR of 24-MAR-2008)	25-MAR-2008 (assigned 27-MAR-2008)
Correspondence (summary of tamper resistance report for AC)	25-MAR-2008 (assigned 27-MAR-2008)
Amendment (CMC data supporting reformulated 60 and 80 mg strengths)	27-MAR-2009 (assigned 10-APR-2009)

*Evaluated in consult review from Arzu Selen, Ph.D., Associate Director of Pharmaceutics.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date (from Form 356h)
Amendment (Response to IR letter of 01-MAY-2009)	13-MAY-2009
Amendment (Provision of SAS stability files for statistician)	29-MAY-2009
Amendment (stability update for 60 and 80 mg strengths)	15-JUN-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Purdue Pharma L.P.

Address: One Stamford Forum
Stamford, CT 06901-3431

Chemistry Review Data Sheet

Representative: Patricia R. Mayer, Ph.D.
Senior Director, U.S. Regulatory Affairs

Telephone: 203-588-7558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: OxyContin® Tablets, extended release
b) Non-Proprietary Name (USAN): oxycodone hydrochloride
c) Code Name/# (OGD only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); refer to cross reference to N20-553 in module 1 or original submission.

10. PHARMACOL. CATEGORY: opioid analgesic

11. DOSAGE FORM: tablet, extended release (code 510)[1]

12. STRENGTH/POTENCY: 10, 15, 20, 30, 40, 60, and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral, code 001

14. Rx/OTC DISPENSED: _X__Rx ___OTC

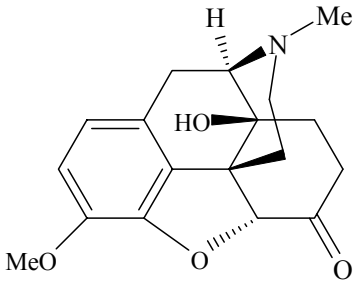
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

[1]The CDER Data Standards Manual does not include a dosage form description for controlled-release tablets, but does include "tablet, extended release" with code 510. The product of N20-553 has the approved name: OxyContin® (oxycodone hydrochloride controlled-release) tablets. As per the instructions from Ali Al Hakim, Ph.D., Branch Chief, at the 09-JUN-2009 meeting, the CMC reviewer informed the review team of the ONDQA recommendation that the applicant change the drug product established name to "oxycodone hydrochloride extended release tablets," to be consistent with current naming policy.

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



HCl

4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4 \cdot HCl$ (crystalline form is actually a monohydrate)
Molecular weight: 351.83 g/mol or 369.84 g/mol as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	29-JUN-2007	Reviewed for another solid oral dosage form product
	4			4	Adequate		Applicant claims on p. 3 of 73 of QOS (orig. submission) that the non-functional tablet coatings have not changed from those previously approved for the previously formulated product. Thus, no further review is necessary. For (b) (4) for 60 and 80 mg strengths, sufficient information is provided in the 27-MAR-2009, amendment.
	3			3	Adequate	12-JAN-2005	In addition, no changes have been made to the CCS as per P.7, relative to the CCS of N20-553.
	3			4	Adequate		See above.
	3			4	Adequate		See above.
	3			4	Adequate		See above.

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	20-553	Purdue Pharma L.P.	original application for OxyContin® Tablets, as supplemented (original approval 12-DEC-1995)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Statistics	Stability data and expiry proposals	17-JAN-2008 (10-40 mg) 15-FEB-2008 (10-40 mg) 20-MAR-2008 (10-40 mg) 23-APR-2009 (60&80 mg) 19-MAY-2009 (10-40 mg) 29-JUN-2009 (60&80mg)	 Final/M. Shen, Ph.D. Final/M. Shen, Ph.D. Final/M. Shen, Ph.D. Final/M. Shen, Ph.D.	24-DEC-2007, amendment adds 9 month stability data; 15-FEB-2008, amendment adds 12 month data; 20-MAR-2008, amendment of dissolution acceptance criteria at 4 h test point 23-APR-2009, amendment provides for two new strengths (60 & 80 mg) with 9 months stability data 13-MAY-2009, amendment adds 18 and 24 month data for 10-40 mg strengths (b) (4) 100, and (b) (4) bottle cts); Note that 29-MAY-2009, amendment provided the data from the 13-MAY-2009, in SAS format 15-JUN-2009, amendment adds 12-24 month stability data
EES		10- and 16-JAN-2008, and 23-APR-2009	Final	OC Recommendation for application is ACCEPTABLE
Pharm/Tox	(b) (4) degradant allowance in DP -residual (b) (4) in (b) (4) excipient	23-APR-2009 18-MAY-2009 (e-mail)	Final/E. Bolan, Ph.D. Final/E. Bolan, Ph.D.	See p. 45 of CMC review #3. See p. 12 of CMC review #4.
Biopharm (ONDQA)	4 hour dissolution acceptance criteria	17-JAN-2008	Final/Arzu Selen, Ph.D.	Original acceptance criteria proposed were wider than (b) (4) of LC for the 4 hour time-point, thus, as per ICH

	10, 15, 20, 30, 40 mg strengths			Q6A, bioavailability data were needed in support of the acceptance range; 07- and 17-MAR-2008, amendments are responses forwarded to consult reviewer; see review of new proposed acceptance criteria on p. 14 of CMC review #2
LNC	N/A			
Methods Validation	N/A			See p. 61 of CMC review #1
DMETS/DDMAC	Labeling/labels			Forwarded by DAARP PM
EA	N/A			See p. 64 of CMC review #1
Microbiology	N/A			See p. 26 of CMC review #1

The Chemistry Review for NDA 22-272

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approval** from the CMC perspective.

To be compliant with current ONDQA policy, it is recommended that the applicant change the drug product established name to "oxycodone hydrochloride extended release tablets" from "oxycodone hydrochloride controlled-release tablets."

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is OxyContin® (oxycodone hydrochloride controlled-release) Tablets and is proposed in strengths of 10, 15, 20, 30, 40, 60, and 80 mg/tablet. The tablets are for oral administration and are packaged (all strengths) in 75 cc HDPE bottles with child resistant caps. The drug product formulation consists of oxycodone hydrochloride (b) (4) polyethylene oxide ((b) (4) by weight) and magnesium stearate (b) (4) by weight (b) (4) The tablets are formed by (b) (4) The applicant claims to have demonstrated the bioequivalence of these newly formulated products to the OxyContin presently approved and marketed under N20-553.

Review of the preliminary report on the applicant's evaluation of the comparative resistance of the newly formulated and the currently marketed product to physical and chemical manipulation lead to the conclusion that the newly formulated product is more manipulation resistant than the current marketed product. However, the determination of the relevance of the *in vitro* preparation conditions

used in the evaluation relative to those used by abusers, and the likely *in vivo* results of usage of such preparations is beyond the scope of this CMC review. The polyethylene oxide polymer is (b) (4) thus it is expected that the formulation would not be susceptible to dose dumping. The is supported by the *in vitro* dissolution data collected (b) (4)

The drug substance is oxycodone hydrochloride monohydrate and it is obtained from a single source that assures the level of the (b) (4) is (b) ( ) The particle size of the drug substance is controlled, although development studies have not shown that variation in particle size leads to variation in drug product performance (e.g., dissolution). Studies reported in the original submission were not able to completely rule out the possibility (b) (4) The most significant variable that impacts the product dissolution is the strength of the tablet. This is not unexpected since the different strengths are not compositionally proportional with respect to the ratio of the active to the excipient components that provide the extended release properties.

The application contained data from a single near-commercial scale (b) (4) batch of each strength, manufactured at the commercial site, and using a process analogous to that intended for commercial production. These batches were used for both the primary stability studies and for the pivotal bioequivalence studies.

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

The labeling indicates that this opioid analgesic should use low initial doses in patients that are not opioid tolerant and especially for those patients receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system active medications. The 60 and 80 mg strengths are said to be for use by opioid tolerant patients only. All of the strengths are to be taken orally at 12 hour intervals. Tablets are to be swallowed whole and are not to be cut, broken, chewed, or crushed, as there is the potential to obtain a fatal dose otherwise. The strengths are 10, 15, 20, 30, 40, 60, and 80 mg.

The application has provided 24 months of stability data for all strengths of the reformulated drug product. An expiry of 24 months is proposed for all strengths and is acceptable.

The storage conditions recommended in the labeling are for room temperature storage in tight containers and with protection from light. The stability data are supportive of these recommendations.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/7/20/09
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
JChen/DAARP/MO
SAlHabet/OCP/Biopharm
DMellon/DAARP/Pharm/Tox TL
EBolan/DAARP/Pharm/Tox
DChristodoulou/ONDQA/DIV I/Branch II/PAL
DHenry/ONDQA/DIV I/Regulatory PM
MShen/DBVI/Math. Stat.

9 pp withheld in full immed. after this page as (b)(4) CCI/TS.

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

/s/

Craig Bertha
7/20/2009 07:31:57 AM
CHEMIST

Ali Al-Hakim
7/23/2009 11:07:45 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-272

OxyContin® (oxycodone hydrochloride controlled-release) Tablets

Purdue Pharma L.P.

Craig M. Bertha, Ph.D.
ONDQA/Division I/Branch 2

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **4**

The Executive Summary **8**

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 10

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment **11**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data **11**

S DRUG SUBSTANCE [oxycodone hydrochloride, (b) (4)] 11

P DRUG PRODUCT [oxycodone hydrochloride tablets, extended release] 11

P.1 Description and Composition of the Drug Product [oxycodone hydrochloride tablets, extended release] 11

P.2 Pharmaceutical Development [oxycodone hydrochloride tablets, extended release] 14

P.3 Manufacture [oxycodone hydrochloride tablets, extended release] 26

P.4 Control of Excipients [oxycodone hydrochloride tablets, extended release] 33

P.5 Control of Drug Product [oxycodone hydrochloride tablets, extended release] 36

P.6 Reference Standards or Materials [oxycodone hydrochloride tablets, extended release] 45

P.7 Container Closure System [oxycodone hydrochloride tablets, extended release] 46

P.8 Stability [oxycodone hydrochloride tablets, extended release] 46

A APPENDICES 54

A.1 Facilities and Equipment (biotech only) 54

A.2 Adventitious Agents Safety Evaluation 54

A.3 Novel Excipients 54

R REGIONAL INFORMATION 54

R1 Executed Batch Records 54

R2 Comparability Protocols 55

R3 Methods Validation Package 55

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 55

A. Labeling & Package Insert 55

B. Environmental Assessment Or Claim Of Categorical Exclusion 57

Chemistry Review Data Sheet

1. NDA 22-272

2. REVIEW #: 3

3. REVIEW DATE: 28-APR-2009

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-NOV-2007 (assigned 17-DEC-2007)
Amendment (stability update)	18-DEC-2008 (assigned 24-DEC-2007)
Amendment (stability update)	15-FEB-2008 (assigned 15-FEB-2008)
Amendment (response to 74-day letter)	06-MAR-2008 (assigned 10-MAR-2008)
Amendment (individual dissolution data)*	07-MAR-2008 (assigned 10-MAR-2008)
Amendment (response to 13-FEB-2008 CMC DR)	13-MAR-2008 (assigned 17-MAR-2008)
Amendment (response to 05-MAR-2008 IR)*	17-MAR-2008 (assigned 19-MAR-2008)
Amendment (response to CMC IR of 24-MAR-2008)	25-MAR-2008 (assigned 27-MAR-2008)
Correspondence (summary of tamper resistance report for AC)	25-MAR-2008 (assigned 27-MAR-2008)

*Evaluated in consult review from Arzu Selen, Ph.D., Associate Director of Pharmaceutics.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC data supporting reformulated 60 and 80 mg strengths)	27-MAR-2009 (assigned 10-APR-2009)

7. NAME & ADDRESS OF APPLICANT:

Name: Purdue Pharma L.P.

Address: One Stamford Forum
Stamford, CT 06901-3431

Chemistry Review Data Sheet

Representative: Patricia R. Mayer, Ph.D.
Senior Director, U.S. Regulatory Affairs

Telephone: 203-588-7558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: OxyContin® Tablets, extended release
b) Non-Proprietary Name (USAN): oxycodone hydrochloride
c) Code Name/# (OGD only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); refer to cross reference to N20-553 in module 1 or original submission.

10. PHARMACOL. CATEGORY: opioid analgesic

11. DOSAGE FORM: tablet, extended release (code 510)[1]

12. STRENGTH/POTENCY: 10, 15, 20, 30, 40, 60, and 80 mg/tablet

13. ROUTE OF ADMINISTRATION: oral, code 001

14. Rx/OTC DISPENSED: _X__Rx ___OTC

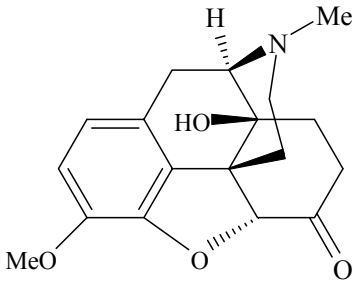
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X____Not a SPOTS product

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

[1]The CDER Data Standards Manual does not include a dosage form description for controlled-release tablets, but does include "tablet, extended release" with code 510. However, the product of N20-553 has the approved name: OxyContin® (oxycodone hydrochloride controlled-release) tablets.



HCl

4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4 \cdot HCl$ (crystalline form is actually a monohydrate)
Molecular weight: 351.83 g/mol or 369.84 g/mol as monohydrate

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	29-JUN-2007	Reviewed for another solid oral dosage form product
	4			4	Adequate		Applicant claims on p. 3 of 73 of QOS (orig. submission) that the non-functional tablet coatings have not changed from those previously approved for the previously formulated product. Thus, no further review is necessary. For (b) (4) for 60 and 80 mg strengths, sufficient information is provided in the 27-MAR-2009, amendment.
	3			3	Adequate	12-JAN-2005	In addition, no changes have been made to the CCS as per P.7, relative to the CCS of N20-553.
	3			4	Adequate		See above.
	3			4	Adequate		See above.
	3			4	Adequate		See above.

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	20-553	Purdue Pharma L.P.	original application for OxyContin® Tablets, as supplemented (original approval 12-DEC-1995)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Statistics	Stability data and expiry proposals	17-JAN-2008 (10-40 mg) 15-FEB-2008 (10-40 mg) 20-MAR-2008 (10-40 mg)	Final/Meiyu Shen, Ph.D.	24-DEC-2007, amendment adds 9 month stability data; 15-FEB-2008, amendment adds 12 month data; 20-MAR-2008, amendment of dissolution acceptance criteria at 4 h test point
		23-APR-2009 (60&80 mg)	Pending	23-APR-2009, amendment provides for two new strengths (60 & 80 mg) with 9 months stability data
EES		10- and 16-JAN-2008, and 23-APR-2009	Pending	Addition of new site for finished dosage form release and stability testing and of raw material testing. EES updated and request for inspection submitted to OC on 23-APR-2009.
Pharm/Tox	oxycodone-*N*-oxide degradant allowance in DP	23-APR-2009	Final/E. Bolan, Ph.D.	See p. 45 of this review.
Biopharm (ONDQA)	4 hour dissolution acceptance criteria 10, 15, 20, 30, 40 mg strengths	17-JAN-2008	Final/Arzu Selen, Ph.D.	Original acceptance criteria proposed were wider than (b) (4) of LC for the 4 hour time-point, thus, as per ICH Q6A, bioavailability data were needed in support of the acceptance range; 07- and 17-MAR-2008, amendments are responses forwarded to consult reviewer; see review of new proposed acceptance criteria on p. 14 of CMC review #2
LNC	N/A			
Methods Validation	N/A			See p. 61 of CMC review #1
DMETS/DDMAC	Labeling/labels			To be forwarded by DAARP PM
EA	N/A			See p. 64 of CMC review #1
Microbiology	N/A			See p. 26 of CMC review #1

The Chemistry Review for NDA 22-272

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval assuming that the applicant adequately addresses the points listed in the attached draft letter and the Office of Compliance issues a recommendation of acceptability for the GMP status of the various associated manufacturing and testing sites.

It is requested that the project manager forward the comments in the attached draft letter to the applicant.

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

No recommendation at this time pending applicant's response to the comments in the attached draft letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is OxyContin® (oxycodone hydrochloride controlled-release) Tablets and is proposed in strengths of 10, 15, 20, 30, 40, 60, and 80 mg/tablet. It is for oral administration and is packaged (all strengths) in 75 cc HDPE bottles with child resistant caps. The drug product formulation consists of oxycodone hydrochloride in a (b) (4) of polyethylene oxide (b) (4) by weight) and magnesium stearate (b) (4) by weight (b) (4) The tablets are formed by (b) (4) The applicant claims to have demonstrated the bioequivalence of this newly formulated product to the OxyContin presently approved and marketed (N20-553).

Review of the preliminary report on the applicant's evaluation of the comparative resistance of the newly formulated and the currently marketed product to physical and chemical manipulation lead to the conclusion that the newly formulated product is more manipulation resistant than the current marketed product. However, the determination of the relevance of the *in vitro* preparation conditions

used in the evaluation relative to those used by abusers, and the likely *in vivo* results of usage of such preparations is beyond the scope of this CMC review. The polyethylene oxide polymer is (b) (4) thus it is expected that the formulation is not susceptible to dose dumping if taken with alcohol, at least based on the *in vitro* dissolution data collected (b) (4)

The drug substance is oxycodone hydrochloride monohydrate and it obtained from a single source that assures the level of the (b) (4) is below (b) (4) The particle size of the drug substance is controlled, although development studies have not shown that variation in particle size leads to variation in drug product performance (e.g., dissolution). Studies reported in the original submission were not able to completely rule out the possibility (b) (4) The most significant variable that impacts the product dissolution is the strength of the tablet. This is not unexpected since the different strengths are not compositionally proportional with respect to the ratio of the active to the excipient components (which provide controlled release properties).

The application contained data from a single near commercial scale (b) (4) batch of each strength, manufactured at the commercial site, and using a process analogous to that intended for commercial production. These batches were used for both the primary stability studies and for the pivotal bioequivalence studies.

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

The labeling indicates that this opioid analgesic should use low initial doses in patients that are not opioid tolerant and especially for those patients receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system active medications. The 60 and 80 mg strengths are said to be for use by opioid tolerant patients only. All of the strengths are to be taken orally at 12 hour intervals. Tablets are to be swallowed whole and are not to be cut, broken, chewed, or crushed, as there is the potential to obtain a fatal dose otherwise. The strengths are 10, 15, 20, 30, 40, 60, and 80 mg.

The application currently provides 12 months of stability data for the 10-40 mg strengths and 9 months of data for the 60 and 80 mg strengths. The applicant proposes a 24 month expiration dating period for all packaging types and for all strengths. The statistical team has reviewed the data for the lower strengths and

states that it only supports an (b) (4) expiry. A consult for a statistical review of the expiry relative to the stability data for the 60 and 80 mg strengths is pending.

The storage conditions recommended in the labeling are for room temperature storage in tight containers and with protection from light. The stability data are supportive of these recommendations.

C. Basis for Approvability or Not-Approval Recommendation

The CMC related issues that are currently unresolved are captured in the attached draft letter. None of these are considered to be issues that can not be easily addressed and resolved, to allow the approval of the application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/4/28/09
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
JChen/DAARP/MO
SAlHabet/OCP/Biopharm
EBolan/DAARP/Pharm/Tox
AAlHakim/ONDQA/DIV I/Branch II/Branch Chief
DChristodoulou/ONDQA/DIV I/Branch II/PAL
DHenry/ONDQA/DIV I/Regulatory PM

58 pp withheld in full immed. after this page as (b)(4) CCI/TS.

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

/s/

Craig Bertha
4/28/2009 01:34:57 PM
CHEMIST

Ali Al-Hakim
4/28/2009 06:14:02 PM
CHEMIST

OXYCONTIN® (OXYCODONE HYDROCHLORIDE CONTROLLED-RELEASE) TABLETS
NDA 22-272

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Indication: OxyContin® is an opioid agonist that is indicated for the management of moderate to severe pain when "around-the-clock" analgesia is needed for an extended time.

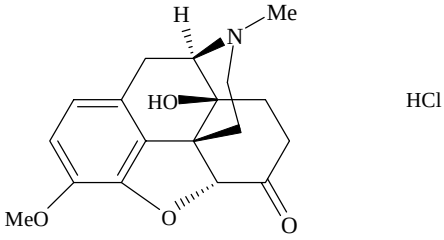
Presentation: Five strengths of 10, 15, 20, 30, and 40 mg oxycodone hydrochloride per tablet.[1] There are (b) (4) count presentations of (b) (4) 100, and (b) (4) tablets for each strength and all are packaged in 75 cc HDPE bottles with child resistant caps.

EER Status: Pending.

Consults: EA – Categorical exclusion provided
Statistics – Consult review received that supports an (b) (4) months expiry period for all presentations of the product in all strengths.
Methods Validation – Deemed not necessary to be forwarded to Agency laboratory.
Microbiology – Deemed not necessary based on water activity data.
ONDQA pharmaceutics – Consult review received.

Original Submission: 28-NOV-2007
Re-submissions: N/A
Post-Approval Agreements: None beyond the typical stability commitment.

Drug Substance: The drug substance oxycodone hydrochloride has the chemical name 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and the structure (reproduced from application), molecular formula, and molecular weight shown below:



[1] In addition to the 10, 15, 20, 30, and 40 mg strengths that are the subject of the application, the proposed label includes information for the older AcroContin® formulated product in the 80 mg strength.

Molecular formula:	$C_{18}H_{21}NO_4$ HCl
Molecular weight:	351.82 g/mol

The drug substance is unchanged from that used for the currently approved and marketed OxyContin® tablet. The drug substance DMF (b) (4)) was reviewed previously and found adequate.

Drug Product: The drug product is OxyContin® (oxycodone hydrochloride controlled-release) Tablets and is proposed in five strengths, 10, 15, 20, 30, and 40 mg/tablet for oral administration. There are (b) (4) count presentations of (b) (4) 100, and (b) (4) tablets for each strength and all are packaged in 75 cc HDPE bottles with child resistant caps. The drug product formulation consists of oxycodone hydrochloride (b) (4) polyethylene oxide (b) (4) by weight) and magnesium stearate (b) (4) by weight). The tablets are formed by (b) (4)

The applicant claims to have demonstrated the bioequivalence of this newly formulated product to the OxyContin presently approved and marketed (N20-553).

Review of the report on the applicant's evaluation of the comparative resistance of the newly formulated and the currently marketed product to physical and chemical manipulation leads to the conclusion that the newly formulated product is more manipulation resistant than the current marketed product. However, the relevance of the *in vitro* preparation conditions used in the evaluation relative to those used by abusers, and the likely *in vivo* results of usage of such preparations are beyond the scope of this CMC review. For details see the evaluation of the report starting on p. 21 of CMC review #1.

The polyethylene oxide polymer is (b) (4), thus it is expected that the formulation is not susceptible to dose dumping if taken with alcohol (*in vitro* dissolution data in the presence of (b) (4) suggest that this will be the case). For details see p. 24 of CMC review #1.

Conclusion: Drug product is satisfactory.

Additional Items: Adequate stability data were provided to support an (b) (4) month expiration dating period for all strengths and packaging presentations. All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding GMPs. Currently, the recommendation is PENDING.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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

/s/

Ali Al-Hakim

4/9/2008 05:42:25 PM

CHEMIST

CHEMISTRY REVIEW

NDA 22-272

OxyContin® (oxycodone hydrochloride controlled-release) Tablets

Purdue Pharma L.P.

Craig M. Bertha, Ph.D.
ONDQA/Division I/Branch 2

Chemistry Review Data Sheet

1. NDA 22-272

2. REVIEW #: 2

3. REVIEW DATE: 04-APR-2008

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-NOV-2007 (assigned 17-DEC-2007)
Amendment (stability update)	18-DEC-2008 (assigned 24-DEC-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (stability update)	15-FEB-2008 (assigned 15-FEB-2008)
Amendment (response to 74-day letter)	06-MAR-2008 (assigned 10-MAR-2008)
Amendment (individual dissolution data)*	07-MAR-2008 (assigned 10-MAR-2008)
Amendment (response to 13-FEB-2008 CMC DR)	13-MAR-2008 (assigned 17-MAR-2008)
Amendment (response to 05-MAR-2008 IR)*	17-MAR-2008 (assigned 19-MAR-2008)
Amendment (response to CMC IR of 24-MAR-2008)	25-MAR-2008 (assigned 27-MAR-2008)
Correspondence (summary of tamper resistance report for AC)	25-MAR-2008 (assigned 27-MAR-2008)

*Evaluated in consult review from Arzu Selen, Ph.D., Associate Director of Pharmaceutics.

7. NAME & ADDRESS OF APPLICANT:

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum Stamford, CT 06901-3431
Representative:	Patricia R. Mayer, Ph.D. Senior Director, U.S. Regulatory Affairs

Telephone: 203-588-7558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: OxyContin® Tablets, extended release
b) Non-Proprietary Name (USAN): oxycodone hydrochloride
c) Code Name/# (OGD only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); refer to cross reference to N20-553 in module 1.

10. PHARMACOL. CATEGORY: opioid analgesic

11. DOSAGE FORM: tablet, extended release (code 510)[1]

12. STRENGTH/POTENCY: 10, 15, 20, 30, and 40 mg/tablet

13. ROUTE OF ADMINISTRATION: oral, code 001

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

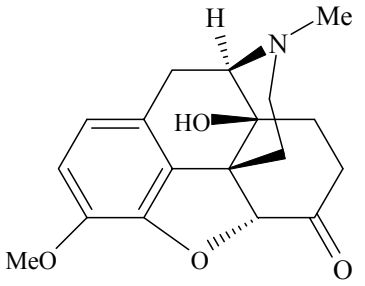
_____SPOTS product – Form Completed

__X____Not a SPOTS product

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

[1]The CDER Data Standards Manual does not include a dosage form description for controlled-release tablets, but does include "tablet, extended release" with code 510. However, the product of N20-553 has the approved name: OxyContin® (oxycodone hydrochloride controlled-release) tablets.

Chemistry Review Data Sheet



HCl

4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4$ HCl
Molecular weight: 351.82 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	29-JUN-2007	Reviewed for another solid oral dosage form product
	4			4	Adequate		Applicant claims on p. 3 of 73 of QOS that the non-functional tablet coatings have not changed from those previously approved for the previously formulated product. Thus, no further review is necessary.
	3			3	Adequate	12-JAN-2005	In addition, no changes have been made to the CCS as per P.7, relative to the CCS of N20-553.
	3			4	Adequate		See above.
	3			4	Adequate		See above.
	3			4	Adequate		See above.

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	20-553	Purdue Pharma L.P.	original application for OxyContin® Tablets, as supplemented

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Statistics	Stability data and expiry proposal	17-JAN-2008 15-FEB-2008 20-MAR-2008	Final/Meiyu Shen, Ph.D.	24-DEC-2007, amendment adds 9 month time-point; 15-FEB-2008, amendment adds 12 month time-point; applicant proposes 24 month expiry; 20-MAR-2008, amendment of dissolution acceptance criteria at 4 h
EES		10- and 16-JAN-2008	Pending	
Pharm/Tox	N/A			
Biopharm (ONDQA)	4 hour dissolution acceptance criteria	17-JAN-2008	Final/Arzu Selen, Ph.D.	Original acceptance criteria proposed were wider than (b) (4) of LC for the 4 hour time-point, thus, as per ICH , bioavailability data were needed in support of the acceptance range; 07- and 17-MAR-2008, amendments are responses forwarded to consult reviewer; see review of new proposed acceptance criteria on p. 14 of CMC review #2
LNC	N/A			
Methods Validation	N/A			See p. 61 of CMC review #1
DMETS/DDMAC	Labeling/labels			To be forwarded by DAARP PM
EA	N/A			See p. 64 of CMC review #1
Microbiology	N/A			See p. 26 of CMC review #1

The Chemistry Review for NDA 22-272

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the application is **recommended for approval**, pending a recommendation of ACCEPTABLE from the Office of Compliance for the establishment evaluations (currently pending).

It is requested that the PM forward the comment included in the draft letter regarding the expiration dating period being granted for the product, based on the analyses conducted by the statistical team.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is OxyContin® (oxycodone hydrochloride controlled-release) Tablets and is proposed in five strengths, 10, 15, 20, 30, and 40 mg/tablet for oral administration. There are (b) (4) count presentations of (b) (4), 100, and (b) (4) tablets for each strength and all are packaged in 75 cc HDPE bottles with child resistant caps. The drug product formulation consists of oxycodone hydrochloride (b) (4) polyethylene oxide ((b) (4) by weight) and magnesium stearate (b) ( ) by weight). The tablets are formed by (b) (4) The applicant claims to have demonstrated the bioequivalence of this newly formulated product to the OxyContin presently approved and marketed (N20-553).

Review of the report on the applicant's evaluation of the comparative resistance of the newly formulated and the currently marketed product to physical and chemical manipulation leads to the conclusion that the newly formulated product is more manipulation resistant than the current marketed product. However, the relevance of the *in vitro* preparation conditions used in the evaluation relative to those used by abusers, and the likely *in vivo* results of usage of such preparations

are beyond the scope of this CMC review. For details see the evaluation of the report starting on p. 21 of CMC review #1.

The polyethylene oxide polymer is [redacted], thus it is expected that the formulation is not susceptible to dose dumping if taken with alcohol (*in vitro* dissolution data in the presence of [redacted] suggest that this will be the case). For details see p. 24 of CMC review #1.

The drug substance is oxycodone hydrochloride monohydrate and it is obtained from a single source that assures the level of the [redacted] is below [redacted] The particle size of the drug substance is controlled, although development studies have not shown that variation in particle size leads to variation in drug product performance (e.g., dissolution). Studies have not been able to completely rule out the possibility [redacted] The most significant variable that impacts on the product dissolution is the strength. This is not unexpected since the different strengths are not compositionally proportional with respect to the active and excipient components, as all strengths have the same total tablet weight of 156 mg (coated).

The application contained data from a single commercial scale [redacted] batch of each strength, manufactured at the commercial site, and using a process analogous to that intended for commercial production. These batches were used for both the primary stability studies and for the pivotal bioequivalence studies.

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

The labeling indicates that this opioid analgesic should use low initial doses in patients that are not opioid tolerant and especially for those patients receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system active medications. The tablets are to be taken orally at 12 hour intervals. Tablets are to be swallowed whole and are not to be cut, broken, chewed, or crushed, as there is the potential to obtain a fatal dose otherwise. Strengths range from 10 – 40 mg, however, there is an 80 mg strength listed in the current proposed labeling that utilizes the older AcroContin® formulation approved for marketing via N20-553.

The application was updated with 9 and then 12 months of stability data and a 24 month expiration dating period is proposed for all packaging types and for both

[2] It is noted that the most current USP monograph for oxycodone hydrochloride drug substance, the minimum standard, lists a limit of not more than 1.0% for individual impurities and not more than 2.0% for the sum of all impurities.

strengths. As a result of the analyses performed by the statistical team, an (b)(4) **month expiration dating period** is granted for all presentations of the product (all strengths, all packaging).

The storage conditions recommended in the labeling are for room temperature storage in tight containers and with protection from light.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/4/4/08
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
AAlHakim/ONDQA/DIV I/Branch II/Branch Chief
DChristodoulou/ONDQA/DIV I/Branch II/PAL
SGoldie/ONDQA/DIV I/Regulatory PM

24 pp withheld in full immed. after this page as (b)(4) CCI/TS

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

/s/

Craig Bertha
4/3/2008 07:30:23 AM
CHEMIST

Ali Al-Hakim
4/4/2008 10:40:37 AM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11-MAR-2008

TO: N 22-272 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Review of Drug Listing Data Elements (DLDE) Table for OxyContin (oxycodone hydrochloride) Tablet, extended release, NDA 22-272

EVALUATION: The DLDE tables for the 10, 15, 20, 30, and 40 mg tablet strengths were reviewed in the SPL and many of the inactive ingredients do not have UNIIs (unique ingredient identifiers), however these are included in the list of pending inactive ingredients that will most likely be assigned UNIIs in the near future (electronic mail message from William A. Hess dated 06-MAR-2008). Aside from this observation, there are no errors in the tables.

ACTION ITEM: NAI

_____
Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:
DAARP/LBasham
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/DChristodoulou
ONDQA/DIV 1/AAl-Hakim_____

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

/s/

Craig Bertha
3/11/2008 10:41:01 AM
CHEMIST

Ali Al-Hakim
3/11/2008 10:42:28 AM
CHEMIST

MEMORANDUM: DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 14-FEB-2008

TO: N 22-272 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ali Al-Hakim, Ph.D.
Branch Chief
ONDQA, Division I, Branch II

SUBJECT: Request from Clinical Pharmacology to finalize the decision on the biowaiver for the 15, 20, and 30 mg strengths of the newly formulated OxyContin (oxycodone hydrochloride controlled-release) Tablets of N22-272

BACKGROUND: The applicant's OxyContin formulation of N22-272 is claimed by the applicant to be more resistant to abuse by tampering than the approved OxyContin drug product of N20-553. The clinical studies included in N22-272 were to demonstrate the bioequivalence (BE) of the new versus the old formulations.

The following response taken from the minutes of the 26-OCT-2006, meeting was provided by the clinical pharmacology team regarding the BE studies proposed by the sponsor:

> *Your proposal for conducting 10-mg and 80-mg BE trials under fed and fasting conditions is acceptable. However, in the light of the lack of proportionality of ingredients between different dose strengths, the bioavailability of 20- and 40-mg OTR tablets should also be assessed. This can be obtained by conducting a dose-proportionality study across all OTR strengths or a fasted BE study comparing 20- and 40-mg OTR tablets and approved tablets.*

However, the sponsor indicated that the development of the 60 and 80 mg strengths was delayed. They then proposed to conduct fasted and fed BE studies for the 10 and 40 mg tablets with a request for biowaivers for the 15, 20, and 30 mg strengths. The clinical pharmacology team (see review from Sally Choe, Ph.D. dated 26-JUN-2007) concluded the following based on the sponsor's proposal and asked that these comments be sent to the sponsor:

> *The biowaiver request for the 15, 20, and 30 mg strengths can be granted once the sponsor submits the following data.*

- *Similar multi-point in-vitro dissolution data of each strength in three dissolution media (e.g., water, 0.1 N HCl, and USP buffer at pH 6.8)*
- *Demonstration of bioequivalence at 10 mg and 40 mg tablets.*

DAARP sent a letter to the sponsor dated 10-AUG-2007, which included the following comments from the clinical pharmacology team:

> *1. Your proposal for a biowaiver for the 15-, 20- and 30-mg strengths is acceptable. However, you need to submit additional in vitro multi-media dissolution information; please see Response #2b below. We note that the completed dose-proportionality study included the 15-, 20- and 30-mg strengths and a biowaiver for these strengths may not be necessary.*
>
> *2.b. In vitro multi-media dissolution data from 10-, 15-, 20-, 30-, 40-, 60-, and 80-mg tablets in pH 4.5 and pH 6.8,*

The clinical pharmacology reviewer concluded in an electronic mail message dated 13-FEB-2007, that all five strengths (10, 15, 20, 30, and 40 mg) were found to be dose proportional in study OTR 1006. Specifically it was stated that:

> *The dose proportionality was conducted using the five strengths (10, 15, 20, 30, and 40 mg). The mean AUC was, 136, 196, 248, 377, and 497 ng·h/mL for the respective strengths. If we normalized each AUC value by the respective dose the ratio remains constant across the strengths as follows:*
>
> *13.6, 13.06, 12.4, 12.5, and 12.4 for 10, 15, 20, 30, and 40 mg strengths, respectively.*
>
> *The same trend is for Cmax.*
>
> *Therefore, we can conclude that the exposure is dose proportional within this dose range.*

EVALUATION: No formal request from the applicant for a biowaiver has been found in the application. However, considering that the clinical pharmacology team indicated in the 10-AUG-2007, letter that because the sponsor was conducting a dose-proportionality study which included the 15, 20, and 30 mg strengths, a "biowaiver for these strengths may not be necessary," and considering the clinical pharmacologist has concluded that the results of that dose-proportionality study showed that the five strengths (including 10 and 40 mg) are dose-proportional, there is no need for a biowaiver. In a follow up electronic mail message from the clinical pharmacology team on 13-FEB-2008, it was concluded that there was no remaining issue with regard to the biowaiver, from their point of view.

It should be recognized, however, that the applicant has provided comparative dissolution data in the pharmaceutical development report (see 2.2.1.7.2 in P.2) at both pH 4.5 and 6.8, as requested by the clinical pharmacology team. (Note that data are also provided at pH 7.5 and in (b) (4) , the latter being the dissolution media used for quality control testing.)

In this study they have compared the dissolution of each strength to both the 10 and 40 mg strengths and have calculated the f2 values. Table 2.2.1.7.4A is reproduced below from p. 42 of 86 of P.2.

It can be seen that all f2 values are above 50, thus the dissolution profiles can be considered to be similar. As an *in vivo/in vitro correlation* (IVIVC) was not established, the importance of this finding is limited and the conclusion of dose proportionality for all of these strengths tested in the dose proportionality study OTR 1006 takes priority.

CMC CONCLUSION/RECOMMENDATION/ACTION ITEM: NAI

_____
Craig M. Bertha, Ph.D.
Chemistry Reviewer

cc:
Orig. NDA 22-272
C.Bertha/ONDQA//Reviewer/2/14/08
AAl-Hakim/ONDQA/Branch Chief_____
DChristodoulou/ONDQA/PAL
LBasham/DAARP/Regulatory PM
SAl Habet/OCP/Reviewer
SDoddapaneni/OCP/TL
ASelen/ONDQA/Assoc. Dir. Pharm.

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

/s/

Craig Bertha
2/14/2008 07:18:38 AM
CHEMIST

Ali Al-Hakim
2/14/2008 01:05:01 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-272

OxyContin® (oxycodone hydrochloride controlled-release) Tablets

Purdue Pharma L.P.

Craig M. Bertha, Ph.D.
ONDQA/Division I/Branch 2

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **4**

The Executive Summary **8**

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 10

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment **11**

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data **11**

S DRUG SUBSTANCE [oxycodone hydrochloride, (b) (4) 11

P DRUG PRODUCT [oxycodone hydrochloride tablets, extended release] 11

P.1 Description and Composition of the Drug Product [oxycodone hydrochloride tablets, extended release] 11

P.2 Pharmaceutical Development [oxycodone hydrochloride tablets, extended release] 14

P.3 Manufacture [oxycodone hydrochloride tablets, extended release] 27

P.4 Control of Excipients [oxycodone hydrochloride tablets, extended release] 33

P.5 Control of Drug Product [oxycodone hydrochloride tablets, extended release] 34

P.6 Reference Standards or Materials [oxycodone hydrochloride tablets, extended release] 53

P.7 Container Closure System [oxycodone hydrochloride tablets, extended release] 53

P.8 Stability [oxycodone hydrochloride tablets, extended release] 53

A APPENDICES 60

A.1 Facilities and Equipment (biotech only) 60

A.2 Adventitious Agents Safety Evaluation 60

A.3 Novel Excipients 61

R REGIONAL INFORMATION 61

R1 Executed Batch Records 61

R2 Comparability Protocols 61

R3 Methods Validation Package 61

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 61

A. Labeling & Package Insert 61

B. Environmental Assessment Or Claim Of Categorical Exclusion 64

Chemistry Review Data Sheet

1. NDA 22-272

2. REVIEW #: 1

3. REVIEW DATE: 25-JAN-2008

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-NOV-2007 (assigned 17-DEC-2007)
Amendment	18-DEC-2008 (assigned 24-DEC-2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum Stamford, CT 06901-3431
Representative:	Patricia R. Mayer, Ph.D. Senior Director, U.S. Regulatory Affairs
Telephone:	203-588-7558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: OxyContin® Tablets, extended release
b) Non-Proprietary Name (USAN): oxycodone hydrochloride

c) Code Name/# (OGD only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); refer to cross reference to N20-553 in module 1.

10. PHARMACOL. CATEGORY: opioid analgesic

11. DOSAGE FORM: tablet, extended release (code 510)[1]

12. STRENGTH/POTENCY: 10, 15, 20, 30, and 40 mg/tablet

13. ROUTE OF ADMINISTRATION: oral, code 001

14. Rx/OTC DISPENSED: _X__Rx ___OTC

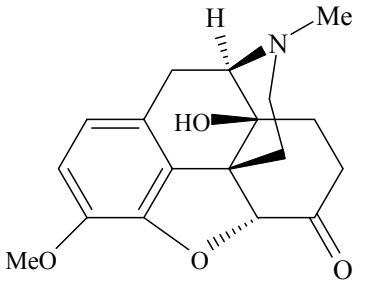
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X____Not a SPOTS product

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

[1]The CDER Data Standards Manual does not include a dosage form description for controlled-release tablets, but does include "tablet, extended release" with code 510. However, the product of N20-553 has the approved name: OxyContin® (oxycodone hydrochloride controlled-release) tablets.

Chemistry Review Data Sheet



HCl

4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Molecular formula: $C_{18}H_{21}NO_4$ HCl
Molecular weight: 351.82 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	2		(b) (4)	3	Adequate	29-JUN-2007	Reviewed for another solid oral dosage form product
	4			4	Adequate		Applicant claims on p. 3 of 73 of QOS that the non-functional tablet coatings have not changed from those previously approved for the previously formulated product. Thus, no further review is necessary.
	3			3	Adequate	12-JAN-2005	In addition, no changes have been made to the CCS as per P.7, relative to the CCS of N20-553.
	3			4	Adequate		See above.
	3			4	Adequate		See above.
	3			4	Adequate		See above.

[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 are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	20-553	Purdue Pharma L.P.	original application for OxyContin® Tablets, as supplemented

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Stability data and expiry proposal	17-JAN-2008	Pending	Application provides 9 months stability and applicant proposes 24 month expiry
EES		10- and 16-JAN-2008	Pending	
Pharm/Tox	N/A			
Biopharm (ONDQA)	4 hour dissolution acceptance criteria	17-JAN-2008	Pending	Criteria proposed is wider than (b) (4) of LC for the 4 hour time-point, thus, as per ICH Q6A, bioavailability data are needed in support of the acceptance range
LNC	N/A			
Methods Validation	N/A			See p. 61
DMETS/DDMAC	Labeling/labels			To be forwarded by DAARP PM
EA	N/A			See p. 64
Microbiology	N/A			See p. 26

The Chemistry Review for NDA 22-272

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable. The comments in the attached draft discipline review letter should be forwarded to the applicant by the project manager.

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

No recommendation at this time pending applicant's response to the discipline review letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is OxyContin® (oxycodone hydrochloride controlled-release) Tablets and is proposed in five strengths, 10, 15, 20, 30, and 40 mg/tablet. It is for oral administration and is packaged (all strengths) in 75 cc HDPE bottles with child resistant caps. The drug product formulation consists of oxycodone hydrochloride (b) (4) polyethylene oxide (b) (4) by weight) and magnesium stearate (b) ( ) by weight). The tablets are formed by (b) (4) The applicant claims to have demonstrated the bioequivalence of this newly formulated product to the OxyContin presently approved and marketed (N20-553).

Review of the report on the applicant's evaluation of the comparative resistance of the newly formulated and the currently marketed product to physical and chemical manipulation leads to the conclusion that the newly formulated product is more manipulation resistant than the current marketed product. However, the relevance of the *in vitro* preparation conditions used in the evaluation relative to those used by abusers, and the likely *in vivo* results of usage of such preparations are beyond the scope of this CMC review. For details see the evaluation of the report starting on p. 21.

The polyethylene oxide polymer is (b) (4), thus it is expected that the formulation is not susceptible to dose dumping if taken with

(b) (4) (*in vitro* dissolution data in the presence of (b) (4) suggest that this will be the case). For details see p. 24.

The drug substance is oxycodone hydrochloride monohydrate and it obtained from a single source that assures the level of the (b) (4) are below (b) (4). The particle size of the drug substance is controlled, although development studies have not shown that variation in particle size leads to variation in drug product performance (e.g., dissolution). Studies have not been able to completely rule out the possibility (b) (4) The most significant variable that impacts on the product dissolution is the strength. This is not unexpected since the different strengths are not compositionally proportional with respect to the active and excipient components, as all strengths have the same total tablet weight of 156 mg (coated).

The application contained data from a single commercial scale ((b) (4) batch of each strength, manufactured at the commercial site, and using a process analogous to that intended for commercial production. These batches were used for both the primary stability studies and for the pivotal bioequivalence studies.

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

The labeling indicates that this opioid analgesic should use low initial doses in patients that are not opioid tolerant and especially for those patients receiving concurrent treatment with muscle relaxants, sedatives, or other central nervous system active medications. The tablets are to be taken orally at 12 hour intervals. Tablets are to be swallowed whole and are not to be cut, broken, chewed, or crushed, as there is the potential to obtain a fatal dose otherwise. Strengths range from 10 – 40 mg, however, there is an 80 mg strength with a different formulation already approved for marketing via N20-553.

The application provides 9 months stability data and they propose a 24 month expiration dating period for all packaging types and for both strengths. A consult to the biometrics team is pending with regard to the appropriateness of the proposed expiry.

The storage conditions recommended in the labeling are for room temperature storage in tight containers and with protection from light.

C. Basis for Approvability or Not-Approval Recommendation

CMC related issues that are currently unresolved are captured in the attached draft letter. None of these are considered to be issues that can not be easily addressed and resolved, to allow the approval of the application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/1/25/08
AAlHakim/ONDQA/DIV I//Branch II/Branch Chief_____

C. CC Block

LBasham/DAARP/Regulatory PM
AAlHakim/ONDQA/DIV I/Branch II/Branch Chief
DChristodoulou/ONDQA/DIV I/Branch II/PAL
SGoldie/ONDQA/DIV I/Regulatory PM

59 pp. withheld in full immed. after this page as (b)(4) CCI/TS.

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

/s/

Craig Bertha
1/28/2008 07:07:29 AM
CHEMIST

Ali Al-Hakim
1/28/2008 01:06:31 PM
CHEMIST

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-272	
Applicant:	Purdue Pharma L.P.	
Stamp date:	November 29, 2007	
PDUFA Date:	May 29, 2008	
Trademark:	Oxycontin®	
Established Name:	Oxycodone Hydrochloride	
Dosage Form:	Extended-release tablets, 10, 15, 20, 30, 40 mg (The firm proposes TR = tamper resistant)	
Route of Administration:	Oral	
Indication:	Management of moderate to severe pain	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(1). OxyContin® (b) (4)" tablets, is a tamper-resistant reformulation of OxyContin® extended-release tablets, NDA 20-553, approved in 1995.

The new formulation has been submitted to IND 29,038 for OxyContin®. It is intended to deter oxycodone abuse potential, by resistance to crushing, chewing and alcohol dose-dumping.

Polyethylene oxide polymer, (PEO), is the key excipient in this new formulation. PEO is a non-ionic, hydrophilic polymer, insoluble in alcohols. Upon contact with water it forms a viscous gel, which renders oxycodone unsuitable for crushing, injecting or snorting. The physical properties of the thermoplastic polymer produced tablets with increased resistance to crushing. These tablets were produced by (b) (4)

The tablets are coated (b) (4) for differentiation. Multiple strengths submitted in this application include 10, 15, 20, 30 and 40 mg. The firm indicated that development of higher strengths is continuing to produce the 60 and 80 mg tablets, so that eventually, all OxyContin® strengths can be replaced in the market with the new formulation, under the current name.

OxyContin® is indicated for the management of moderate to severe pain and is dosed twice daily.

Oxycodone is a pure μ receptor agonist, involved in pain responses. OxyContin® tablets will be packaged in (b) (4) cc white HDPE bottles, sealed with a heat induction seal, and a (b) (4) child resistant closure (b) (4) The proposed bottle will be filled with tablet counts of (b) (4), 100 (b) (4) tablets at the time of submission. (b) (4)

B. Review, Comments and Recommendations

Drug Substance

(b) (4)

10 pp withheld in full immed. after this page as (b)(4) CCI/TS.

Labeling
Provided in M1. Labeling information on the container labels and packaging insert should be assessed with respect to CMC related information.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF (b) (4) should be reviewed and evaluated. Process capability regarding the (b) (4) should be assessed. The suitability of these limits for drug product manufacture should be evaluated as per the EMEA Guideline in consultation with the Toxicology Division.
2. The drug substance acceptance specifications by Purdue Pharma and future manufacturer qualifying criteria should be requested so that they wil be included in the NDA.
3. The excipients specifications and physical attributes and their suitability for drug product manufacturability, quality and performance should be assessed.
4. The specification for (b) (4) limit in the excipient (b) (4) should be assessed in consultation with the Toxicology Division.
5. Impact of physical properties of the drug substance, e.g., solubility, polymorphism, particle size distribution, etc., on the formulation ((b) (4), should be assessed on manufacturability, quality and drug product performance through the propsed shelf-life.
6. (b) (4)
7. The report on evaluation of the resistance to physical and chemical alteration should be assessed from CMC perspective, (b) (4)
8. Hold times of drug product intermediates should be assessed based on stability data.
9. The dissolution method should be assessed for discriminatory ability and robustness, e.g., by supporting data on developmental formulations. Conclusions from supporting *in-vivo* studies should be discussed with the Clinical Pharmacology Division.
10. Expiration dating and justification based on statistical analysis should be assessed in consultation with the Statisticians.
11. The dissolution specification, selection of batches and statistical analysis of the dissolution data should be assessed in consultation with the Statisticians.
12. The dissolution profiles of the reformulated OxyContin® and comparisons with the current product should be assessed with respect to the sponsor's claim that the new formulation has less alcohol dose dumping potential.

D. **Comments for 74-day Letter**:

- Provide statistical analysis of the stability and dissolution test data in SAS format during early stage of the review cycle.
- Identify the packaging components that are supplied by (b) (4), holder of DMF (b) (4).
- Provide the master batch (blank) records for the lowest (10 mg) and highest (40 mg) tablets.

E. **Recommendation for fileability**: The NDA is fileable based on agreement with the Agency to submit one batch of each reformulated strength with 6-month stability data under long term and accelerated storage. The firm amended the 9-month long term data on 12/20/07.

Recommendation for Team Review: The NDA is not recommended for team review, since it is a reformulation, the drug substance is not an NME and the manufacturing process comprises of standard operations. However, the primary reviewer should assess the manufacturing process and reformulation accounting for the overall profile regarding resistance to alcohol dose dumping and resistance of abuse by physical and chemical means of oxycodone extraction and destruction procedure of the extended-release (b) (4) (PEO).

Consults
Specifications for impurities and degradation products should be evaluated in consultation with the Toxicology reviewer.
The primary reviewer, in conjunction with the project manager, should initiate a consult of the dissolution specification, stability data as soon as possible (see fileability template below).

Danae D Christodoulou, Ph.D. 1/15/2008
Pharmaceutical Assessment Lead Date

Ali Al-Hakim, Ph.D. 1/16/2008
Branch II Chief, ONDQA Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion claimed as per 21 CFR 25(b)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	NA		Solid oral dosage form/ extended-release
16	Have all consults been identified and initiated?	√ √ √ NA NA √ NA		Pharm/Tox Biopharm Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

(b) (4)	LoA Included	Status
	Yes	pending
	Yes	pending
	Yes	NA
	Yes	NA
	Yes	NA
	Yes	NA

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

/s/

Danae Christodoulou
1/16/2008 01:11:57 PM
CHEMIST
Initial Quality Assessment

Ali Al-Hakim
1/16/2008 01:23:20 PM
CHEMIST

REV-QUALITY-04 (Review Noted (NAI))
NDA-022272
ORIG-1
Supporting Document 22
Quality/Quality Information
Submit Date: 04/23/2008 - FDA Received Date: 04/23/2008

Refer to CMC review of 23-JUL-2009

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22272	ORIG 1	PURDUE PHARMA INC	OXYCONTIN

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

/s/

CRAIG M BERTHA
07/27/2009