CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208090Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
NDA: Approval

NDA 208090
Review 2
Review Date

Drug Name/Dosage Form	Xamptza (Oxycodone) ER Capsules
Strength	9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Collegium Pharmaceutical, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	None	OPQ/ONDP/DNDPAPI/BII
Drug Product	Xiaobin Shen	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta	OPQ/OPF/DPAII/BVI
Microbiology	Tarun Mehta	OPQ/OPF/DPAII/BVI
Facility	Christina Capacci-Daniel/Derek Smith	OPQ/OPF/DIA/BII
Biopharmaceutics	Fang Wu/ John Duan	OPQ/ONDP/DB/BIII
Project/Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead		
Environmental Assessment (EA)		

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This resubmission comprising two amendments provides for a comparability protocol (b) (4) Sufficient data is provided to demonstrate the continued quality of the drug product, manufactured (b) (4) Data for the (b) (4) kg scale, is provided and has been reviewed by Drug product, Process and Biopharm. No changes to the drug substance are proposed in this resubmission. All three offices recommend approval of the amendments and the NDA resubmission. (b) (4)

Further, the facilities reviewer has recommended the facilities as adequate.

No changes to the drug product composition, release or storage conditions are proposed. Therefore the abuse deterrence assessment of Catgory 1 studies, are referenced to Review 1 of this NDA.

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

The Sponsor has agreed to provide process data,to demonstrate adequate control of particle size in a Special Report postapproval. (See Review by the Process Group, attached).

II. Summary of Quality Assessments

A. Drug Substance

None. No changes to the Drug Substance section since review of the orginal submission in September 2015.

B. **Drug Product** No change to the product (b) (4)

C. Biopharmaceutics Considerations

See Attached review

D. **Process/Facility Quality Summary**

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(b) (4)

Reviewer: Tarun Mehta, 4/16/2016

ASSESSMENT OF THE BIOPHARMACUETICS

BIOPHARMACEUTICS REVIEW **Office of New Drugs Products**			
Application No.:	NDA 208090	**Primary Reviewer:** Fang Wu, Ph.D.	
Division:	DAAAP		
Applicant:	Collegium Pharmaceutical, Inc.	**Secondary Reviewer:** John Duan, Ph.D.	
Trade Name:	Xtampza ER™	**Biopharmaceutics Branch Chief (acting):** John Duan, Ph.D. Angelica Dorantes, Ph.D.	
Generic Name:	Oxycodone extended-release capsules	**Biopharmaceutics Division Director(acting):** Paul Seo, Ph.D.	
Indication:	Management of severe pain	**Date Assigned:**	February 18, 2016
Formulation/strength	Oxycodone extended-release capsules, 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg oxycodone HCl	**Date of Review:**	April 14, 2016
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission dates	**Date of informal/Formal Consult**	**PDUFA DUE DATE**
February 17, 2016	February 18, 2016	N/A
Type of Submission:	Amendment to NDA 208090	
Key issues:	Similarity comparisons between the dissolution profiles obtained from the (b) (4) kg commercial scale batch for manufacturing Xtampza ER™ Capsules (Oxycodone extended-release capsules (b) (4)) and that obtained from the tentatively approved	

	manufacturing scale ((b) (4) kg) batch.

Background:

NDA 208090 for Xtampza ER™ (oxycodone) extended-release capsules, received tentative approval on December 8th, 2015 for (b) (4) kg scale. Following tentative approval, Collegium (b) (4) Pharmaceutical, Inc. submits an amendment to NDA 208090, SN 0050, containing information pertaining to this batch for the final approval to manufacture drug product, Xtampza ER™, Oxycodone extended-release capsules, at the (b) (4) kg scale. The is also to respond to FDA's information request dated 07/08/2015, which reads "multipoint dissolution profiles should be obtained in three media, in addition to performing the application/compendial release requirements, in order to demonstrate comparability of batches produced at the (b) (4) kg and (b) (4) kg scales".

According to the Applicant, (b) (4) kg scale drug product physicochemical properties including particle sizes, dissolution profiles, release specification, (b) (4) and abuse deterrent properties remain unchanged from the tentatively approved NDA (b) (4) kg scale except administrative changes.

Review:

This review is focused on similarity comparisons between the dissolution profiles obtained from the (b) (4) kg commercial scale batch for manufacturing Xtampza ER™ Capsules (Oxycodone extended-release capsules, (b) (4)) and that obtained from the tentatively approved manufacturing scale ((b) (4) kg) batch.

RECOMMENDATION:

ONDP-Biopharmaceutics has reviewed the amendment to NDA 208090 submitted on February 17, 2016. The provided data support the acceptability of the (b) (4) kg commercial batch for (b) (4) Xtampza ER™ Capsules (Oxycodone extended-release capsules). (b) (4) after the internal discussion within biopharmaceutics review team and with the CMC review team, no further dissolution profiles comparisons data are requested (b) (4) prior to the approval.

Therefore, from the biopharmaceutics perspective, commercial products at (b) (4) kg scale for 9, 13.5, 18, 27 and 36 mg strength oxycodone extended-release capsules are recommended for APPROVAL .

SIGNATURE BLOCK

Fang Wu, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drugs Products

Date: 4/14/2016

John Duan, Ph. D
Secondary Reviewer and Branch Chief (acting)
Division of Biopharmaceutics
Office of New Drugs Products

Date: 4/12/2016

Paul Seo, Ph. D
Tertiary Reviewer and Division Director (acting)
Division of Biopharmaceutics
Office of New Drugs Products

Date: 4/15/2016

cc : Sandra, Suarez, Angelica Dorantes

Biopharmaceutics Evaluation

I. Background

Following the receipt of Tentative Approval of NDA 208090, (b) (4)

Applicant submitted data (b) (4)

II. Dissolution profile comparisons

Comparative dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches in 3 different media are included with this submission. Based on the Applicant's similarity analyses, all f2 values are more than 50 (b) (4) using the tentatively approved dissolution method shown below. The results are shown in **Table 1** and **Figure 1-3**.

Parameter	Selection
Apparatus	USP I (Baskets)
Agitation Speed	100 RPM
pHs (Buffer)	*Medium #1:* (b) (4) *Medium #2: 4.5 (USP Sodium Acetate) with surfactant* *Medium #3:* (b) (4)
Surfactant	Tween 20
Surfactant Level	0.03%
Volume	900 mL
Temperature	37°C

Table 1. Dissolution Comparison Test Results in Three Dissolution Media for (b) (4) kg Registration/Bio-batch Scale and Proposed Commercial (b) (4) kg Scale

Media	Sample Information	Mean% Dissolved (% D)[1] Std. Dev. (sd)	Test Time Point (hr)	f2 (b) (4)
Medium #1 (b) (4)	(b) (4) kg Lot # 3104085R	% D		
		sd		
	(b) (4) kg Lot# 3132667R	% D		
		sd		
Medium #2 (pH 4.5 Acetate)	(b) (4) kg Lot # 3104085R	% D		
		sd		
	(b) (4) kg Lot# 3132667R	% D		
		sd		
Medium #3 (b) (4)	(b) (4) kg Lot # 3104085R	% D		
		sd		
	(b) (4) kg Lot# 3132667R	% D		
		sd		

[1]. Individual % oxycodone dissolved data located in Appendix B in the responses to information request dated 11/20/2015.(\\cdsesub1\evsprod\nda208090\0050\m1\us\111-information-amendment\quality-information-amendment\response-to-information-request-dated-no.pdf)

Figure 1. Medium #1 (b) (4): Dissolution Profile Comparison

(b) (4)

Figure 2. Medium #2 (pH 4.5 Acetate with 0.03% Tween 20): Dissolution Profile Comparison

Figure 3. Medium #3 (b) (4): Dissolution Profile Comparison

Reviewer's Assessment:

- *The submitted data demonstrated the similarity of the release of Oxycodone in three media ((b) (4), pH 4.5 sodium acetate buffer with 0.03% Tween-20 [QC release media], and pH*

[redacted]) between [redacted] kg scale (commercial batch size) and [redacted] kg batch (biobatch), f2 are all>50.

III. Additional supports

The additional supporting evidences submitted by the Applicant are listed below:

- The [redacted] kg scale batch [redacted] passed the [redacted] finished product release specifications as the [redacted] kg scale batches. The results are shown in **Table 2**.
- [redacted]
- Abuse deterrent properties [redacted] remain unchanged for [redacted] kg scale batch when compared to the tentatively approved NDA [redacted] kg scale. The results are shown in **Table 3-4 and Figure 4-5**.

Table 2. Summary of Batch Release Data for [redacted] kg Registration/Bio-batch Scale and Proposed Commercial [redacted] kg Scale

Test	Release Acceptance Criteria			[redacted] kg Batch Results[1]				[redacted] kg Batch Results
				Capsule lot 3100363R	Capsule lot 3104085R	Capsule lot 3104086R	Capsule lot 3104087R	Capsule lot 3132667R
Content Uniformity cUSP <905> Acceptance Criteria	[redacted]							
Dissolution cUSP <711> Acceptance Criteria	1 hour	[redacted]%	Mean (n=12) Range					
	4 hours	[redacted]%	Mean (n=12) Range					
	12 hours	NLT [redacted]%	Mean (n=12) Range					

1 Filed in NDA submission; referred to as Clinical Trial Batch, Registration batch 1, Registration batch 2, and Registration batch 3, respectively.

Table 3. Abuse Deterrent Property Comparison Test Results for [redacted] kg Registration/Bio-batch Scale and Proposed Commercial [redacted] kg Scale

Test	Conditions	Summary Result (Comparing [redacted] kg Scale Batch to [redacted] kg Scale Batch	Representative Figures

Category 1 *in vitro* abuse-deterrence tests	Crushing using 3 different household utensils (i.e., mortar and pestle, coffee grinder and food chopper) followed by dissolution testing	Similar dissolution profiles after crushing with 3 household utensils (f2 greater than 50; values of 77, 67, and 64 for mortar and pestle, coffee grinder and food chopper, respectively)[1]	Figure 4
	Extraction using 3 ingestible solvents (i.e., water, vinegar and 40% ethanol) at room temperature through 24 hours	Comparable extraction profiles when comparing (b) (4) kg scale batch with (b) (4) kg scale batch in water, vinegar and 40% ethanol	Figure 5
	Small volume extraction in water at 90-95°C through 5 minutes (preparation for IV injection)	Comparable amount of drug extracted across 3 time points when comparing (b) (4) kg scale batch with (b) (4) kg scale batch	Table 4

[1] Dissolution conducted in QC media, pH 4.5 sodium acetate buffer with 0.03% Tween 20 (n=6)

Figure 4. Dissolution Profile Comparison after Crushing with Mortar and Pestle

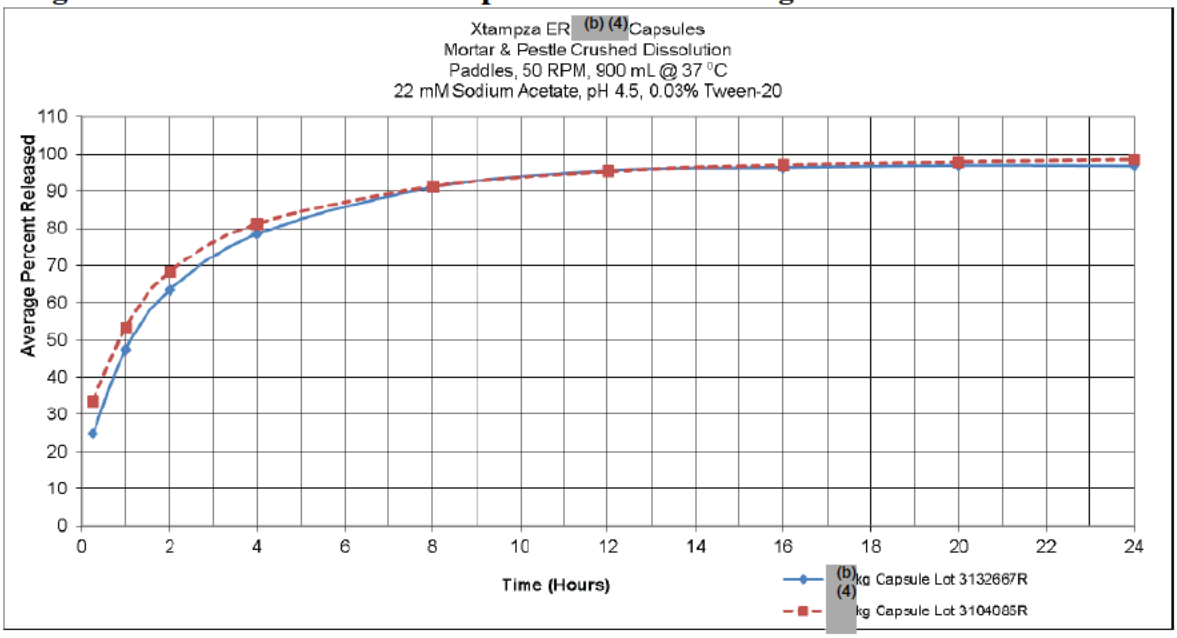

Figure 5. Extraction Comparison with Water at Room Temperature

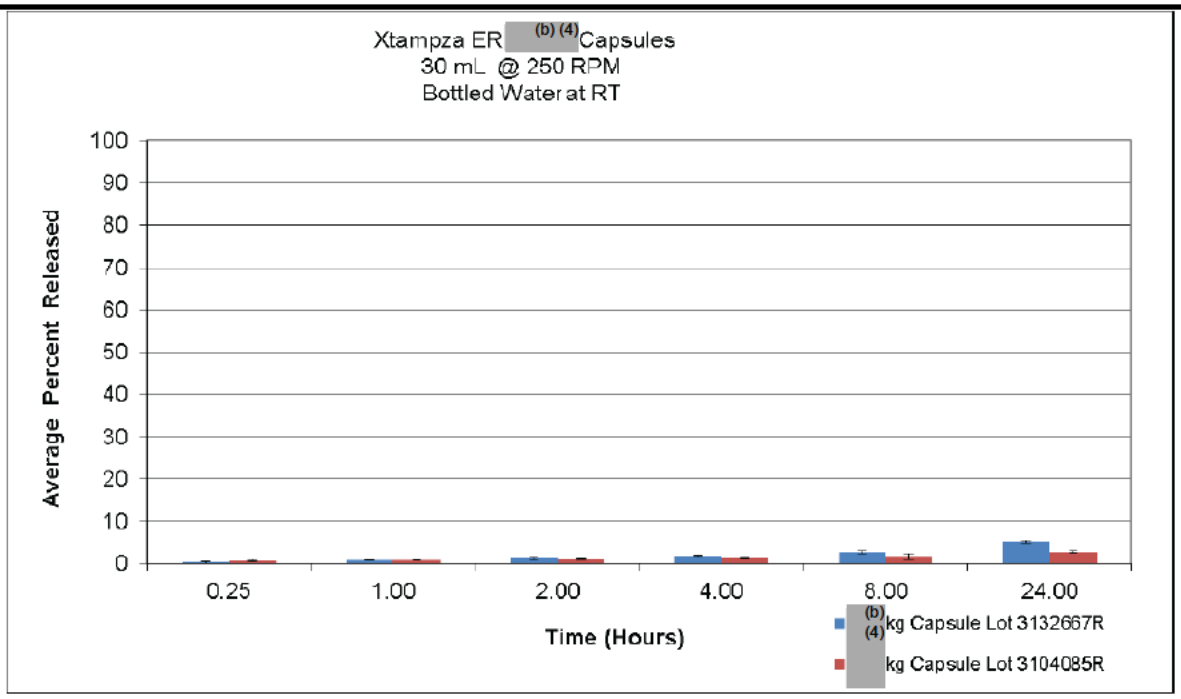

Table 4. Small Volume Extraction Results in Water for Three Different Extraction Times

Extraction Time	Sample Information	0.5 Minutes	2 Minutes	5 Minutes
Average Filtered Volume Collected (mL)[1]	(b) (4) kg Lot # 3104085R	5.0	4.9	4.7
	(b) (4) kg Lot# 3132667R	4.3	4.4	4.4
Average Amount of Drug in Filtered Solution (mg)[2]	(b) (4) kg Lot # 3104085R	1.4	1.8	1.8
	(b) (4) kg Lot# 3132667R	1.2	1.8	2.1
Average % Label Claim in Filtrate	(b) (4) kg Lot # 3104085R	3.6	4.4	4.5
	(b) (4) kg Lot# 3132667R	3.0	4.6	5.4

[1] Individual replicate data located in Appendix B
[2] Amount of drug is reported as oxycodone HCl equivalent in order to be consistent with data filed in the NDA submission

Reviewer's Assessment:

- *The (b) (4) kg scale batch (b) (4) passed the (b) (4) finished product release specifications as the (b) (4) kg scale batches (1 hour, (b) (4)%; 4 hours, (b) (4)% and 12 hours, NLT (b) (4)%).*

- *The Abuse deterrent properties for (b) (4) kg scale batch (b) (4) are comparable to the tentatively approved (b) (4) kg scale.*
- *The dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches for oxycodone extended-release capsules, (b) (4) are similar (f2>50, refer to **Table 1** in APPENDIX).* (b) (4) *the following IR was issued on 3/17/2016.*

IR#1

1. You have submitted data showing dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches for (b) (4) oxycodone extended-release capsules are similar (f2>50). (b) (4)

Responses from the Applicant dated 03/18/2016 is summarized below:

1. The Applicant (Collegium) submitted data showing dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches for (b) (4) oxycodone extended-release capsules are similar (f2>50) (b) (4)

2. Collegium intends to submit (b) (4)

Reviewer's Assessment:

Based on our internal discussion and the discussion with CMC product reviewer and process reviewer, (b) (4) kg batch size for 9, 13.5, 18, 27 mg and 36 mg strength (all the strengths) is recommended for APPROVAL based on the current submitted data. The reasons are summarized below:

- Dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches for (b) (4) oxycodone extended-release capsules are similar in three tested media (pH (b) (4) 4.5 and (b) (4)) (f2>50).
- For (b) (4) kg batch size, the dissolution profiles (b) (4)

(b) (4) are similar in all tested media (pH (b) (4) 4.5 and (b) (4)).

- The particle size of microspheres is controlled within reasonable limits during the manufacturing process for (b) (4) kg scale.
- (b) (4)
- The Applicant commits to submit (b) (4) in a special report in the responses dated 04/14/2016, which is in response to the information request (IR) by the Agency dated 04/12/2016.

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Chemistry Review #2 for NDA 208090

October 7, 2015

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This drug product is recommended for approval from the Chemistry, Manufacturing, and Control (CMC) perspective.

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

A PMC was agreed to by the Sponsor (October 2, 2015) to manufacture only on an exhibit/registration batch scale of (b) (4) kg. Further, the Sponsor also committed to provide commercial scale data in a Prior Approval Supplement, prior to implementing the manufacture of the (b) (4) kg commercial batch scale.

C. Outstanding Issues from Review 1 of the Drug Product(s) and Drug Substance(s)

1. Facilities inspection is adequate. Office of Process and Facilities has updated their review to reflect a satisfactory recommendation from the Office of Compliance.

2. Outstanding agreement to the PMC in item IB above. The Sponsor has committed to not begin commercial manufacturing, until approval of the commercial scale process data, to be submitted in a Prior Approval Supplement.

3. Updated Carton labels have been submitted to reflect the changes requested by the Agency. The Sponsor neglected to delete the art work above the Xtampza name. DMEPA has given their concurrence to allow the art work above the name.

B. Endorsement Block

Ciby J. Abraham, Ph.D., Acting Quality Assesment Lead (On Leave)

Julia C. Pinto, Ph.D., Acting Branch Chief, OPQ/ONDP Division II/Branch IV

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.10.07 18:45:38 -04'00'

QUALITY ASSESSMENT

Recommendation:
NDA: Approval for registration batch size ((b) (4) kg) with Prior approval supplement for commercial scale ((b) (4) kg) batch.

See the list of deficiencies at the end of the review

NDA 208090
Review # 1
Review Date 9/25/2015

Drug Name/Dosage Form	Oxycodone DETERx, Extended release Capsules
Strength	10mg, 15mg, 20mg, 30mg and 40mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Collegium Pharmaceutical, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE
SN 0000	12/12/2014
SN 0006	2/11/2015
SN 0018	05/01/2015
SN 0025	07/29/2015
SN 0030	08/11/2015
SN 0031	08/26/2015
SN 0034	09/22/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Process	Tarun Mehta	VI/2
Microbiology	Tarun Mehta	VI/2
Facility	Tarun Mehta/ Robert Wittorf	VI/2 and II/5

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OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

The applicant has submitted a detailed Product Development Report describing their strategy for developing an adequate manufacturing process. Prior to the process development study, the applicant evaluated the initial risks involved with each unit operation (b) (4) After studying these risks, bench and pilot scale process development batches were manufactured to evaluate each unit operation. (b) (4)

(b) (4) The manufacturing process includes the following unit operations: (b) (4)

Using the developed process, the applicant has successfully manufactured the drug product at (b) (4)kg scale. To study the technology transfer of pilot scale manufacturing to commercial scale manufacturing, the applicant has manufactured one placebo batch at (b) (4)kg batch size.

The manufacturing information submitted at pilot scale ((b) (4)kg) is adequate. The pilot scale batches were manufactured (b) (4)

The pilot batches met all (b) (4) and the release and stability data of these batches are satisfactory. The applicant should apply and qualify (b) (4) during validation.

The applicant has proposed a (b) (4)kg batch size for commercial manufacturing. However, the proposed commercial manufacturing process includes many changes (b) (4) (b) (4) The applicant has provided an explanation of these changes in their IR responses and some experimental data to justify the changes to the process. However, additional development work is necessary to demonstrate viability of the commercial process. Also, the applicant has not provided release and stability data of this pre-validation commercial batch and it does not meet the dissolution specifications recommended by Biopharm. For example, the pre-validation commercial batch did not meet (b) (4)

Based on the PAI finding and results of trial manufacture of one commercial scale batch, it is clear that the applicant does not have full understanding of the manufacturing process at each unit operation. During PAI inspection applicant suggested that they will need to (b) (4)

(b) (4) Batches manufactured at commercial scale (b) (4) should meet the biopharm requirements. (see Biopharm deficiency). See below the rational for final approval to be communicated with the applicant.

Approval recommendation to be communicated with the applicant:

I. Approval at exhibit batch scale ((b) (4)kg):
The NDA submission has provided sufficient manufacturing information to establish the process defined in the NDA for the manufacture of exhibit batch ((b) (4)kg). This same process, (b) (4) may therefore be used by the applicant for commercial production at (b) (4)kg scale. For successful validation at this scale, it is recommended that the applicant (b) (4)

II. Prior Approval Submission for proposed commercial scale batches ((b) (4)kg):
Based on the PAI inspection findings and data submitted in subsequent amendments, FDA is not convinced that applicant has complete understanding and knowledge to manufacture commercial scale batches with all the proposed changes. We find that additional product development work is necessary (b) (4) A clear understanding of the (b) (4) are needed in order to produce desired quality product. We recommend that the applicant establish (b) (4) for successful commercial scale manufacturing. We are not convinced (b) (4) It should be noted that the clinical batches were produced under these conditions.

If the applicant desires (b) (4) the proposed commercial scale ((b) (4)kg) batch, they should submit the detailed information of commercial scale manufacturing process including but not limited to the (b) (4) with adequate justification. Also batch records and all other applicable quality control data, including bio pharm requirement for dissolution of all commercial batches should be submitted in a Prior Approval Supplement.

Tarun Mehta, Chemist
09/25/2015

Supervisor Comments and Concurrence:
Concur with recommendation to approve NDA manufacturing process and controls at batch size of (b) (4)kg and PAS for (b) (4)kg
Ubrani V. Venkataram, 25-Sep-2015

QUALITY ASSESSMENT

NDA 208-090
Review # 1
Review Date 09/08/2015

Drug Name/Dosage Form	Oxycodone Extended Release (XTAMPZA) Capsule
Strength	9, 13.5, 18, 27 and 36 mg (Oxycodone base, equivalent to 10, 15, 20, 30 and 40 mg of Oxycodone HCl)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Collegium Pharmaceutical
US agent, if applicable	None

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission - 0000	12/12/2014
Amendment - 0006	2/11/2015
Amendment - 0025	7/29/2015
Amendment - 0027	8/7/2015

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY	BRANCH/DIVISION
Drug Substance	Xavier Ysern	Donna Christner, Ph.D	Branch II/ONDP
Drug Product	Xiaobin Shen, Ph.D.	Julia Pinto, Ph.D.	Branch IV/ONDP
Process	Tarun Mehta, Ph.D.	Ubrani Venkataram, Ph.D.	OPF
Microbiology	Tarun Mehta, Ph.D.	Ubrani Venkataram, Ph.D.	OPF
Facility	Robert Wittorf	Mahesh Ramanadham, PharmD	OPF
Biopharmaceutics	Fang Wu, Ph.D.	John Duan, Ph.D.	Branch III/ONDP
Project/Business Process Manager	Steven Kinsley, Ph.D.	N/A	OPRO
Application Technical Lead	Ciby Abraham, Ph.D.	N/A	Branch II/ONDP

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	7/16/2015	
	Type IV			NA		There is enough information in the NDA.
	Type III			NA		There is enough information in the NDA
	Type III			NA		There is enough information in the NDA.
	Type III			NA		
	Type III			NA		

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
PreNDA meeting	IND 75,786	Meeting minutes

3. CONSULTS:

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

Executive Summary

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendation from the following disciplines; drug substance, biopharmaceutics, and drug product; CMC recommends the approval of Xtampza extended-release 10, 15, 20, 30, and 40 mg capsules pending the overall recommendation from the Office of Compliance, Microbiology, and Process.

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

N/A

II. Summary of Chemistry Assessments

A summary of each disciplines review is shown below.

Drug Substance

The drug substance, Oxycodone Base is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 7/16/2015). Oycodone is a white to off-white powder with a log P (octanol/water neutral species) of 1.743 and soluble in water across a pH range of 0.994 to 11.743, and ranged from 173 mg/mL to 0.164 mg/mL, respectively. Polymorph screening identitfied (b) (4) Oxycodone base is not hygroscopic. The drug substance has a (b) (4) month retest period when stored in a (b) (4) container/closure at (b) (4) °C, excursion permitted to (b) (4) °C.

Drug Product

The drug product Xtampza ER is manufactured by Patheon, Inc. The capsules are manufactured in five capsule strengths containing 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg of oxycodone base, which is equivalent to 10, 15, 20, 30, and 40 mg of oxycodone HCl. (b) (4) The oxycodone capsule formulation contains microspheres with a median particle size of approximately (b) (4) microns.

Xtampza capsules are packaged in 100-count, round, white, high-density polyethylene bottles of different sizes depending on the capsule strength; bottle sizes of 60 cc, 100 cc, 120 cc, 150 cc and 200 cc are used for the 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxycodone HCl-equivalent strengths, respectively. The bottles are (b) (4) capped with (b) (4) child-resistant caps. Based on the stability data provided, an expiry of 24-months will be granted using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature]". For the in-vitro abuse deterrence studies, the summary of all the studies can be found in the Drug Product chapter on page 7. Based on the totality of the in-vitro abuse deterrence studies, it appears that Xtampza capsules show better in-vitro abuse deterrent properties than Oxycontin OP ER and Roxicodone in terms of resisting particle size reduction, less drug efficiency and recovery during the syringeability tests, and lower recoveries by a wide range of extraction methods.

Process - Pending

Microbiology – Pending

Facilities - Pending

Biopharmaceutics

According to the applicant, oxycodone base is a BCS (Biopharmaceutical Classification System) Class III compound (high solubility/low permeability). The dissolution method and acceptance criteria are acceptable for this application. (b) (4) The applicant has performed in-vitro alcohol dose dumping studies using 0%, 4%, 20%, and 40% ethanol through 24 hours, which shows it is not likely alcohol induced dose dumping will occur.

Based on dissolution profile comparisons between the products with and without PSR (particle size reduction), Xtampza shows better abuse

deterrent property than OxyContin OP ER product. See page Biopharm-30 for more details.

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

Xtampza is an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone. The formulation provides analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, biopharmaceutics, and drug product. The application is therefore recommended for approval pending the overall recommendation from the Office of Compliance, Microbiology, and Process.

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	Acceptable	Stability: The drug product is granted a 24 month expiry at 25 °C. (b) (4) is observed but within specification.
Physical stability (API)	• Formulation • Raw materials • Process parameters	L	-	N/A	-

	• Scale/equipment • Site				
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	-	-	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	M	-	Acceptable	Based on the Risk Assessment and development work, it seems that the particle size will affect to dissolution CQA. However, a discriminatory dissolution method has been developed, decrease the difficulties of detectability.
Alcohol Dose Dumping	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	M	-	Acceptable	There is no dose dumping detected in the in vitro dose dumping study under the condition tested. In vivo alcohol dose dumping study data confirmed that there is no dose dumping issues.

*Risk ranking applies to product attribute/CQA

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

III. Administrative

A. Reviewer's Signature

Ciby J. Abraham -S

Digitally signed by Ciby J. Abraham -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -S
Date: 2015.09.09 07:01:50 -04'00'

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

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

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: XTAMPZA ER Established Name: Oxycodone extended-release capsule	Acceptable. Note that the final proprietary name has not been updated yet in the package insert. Acceptable
Dosage form, route of administration	Dosage: Capsule Route: Oral	Acceptable Acceptable
Controlled drug substance symbol (if applicable)	CII	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	See above in the reproduced highlights section.	Acceptable

Conclusion: Acceptable. The correct proprietary name will be updated before an approval action is taken.

(b) "Full Prescribing Information" Section

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

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Extended-release capsules	Acceptable
Strengths: in metric system	9 mg, 13.5 mg, 18 mg, 27 mg and 36 mg oxycodone (base) equivalent to 10 mg, 15 mg, 20 mg, 30 mg and 40 mg oxycodone HCl	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	• Each 9 mg extended-release capsule has an ivory cap with (b) (4) (b) (4) printed on it and a white body; each 9 mg capsule contains the equivalent of 10 mg oxycodone HCl • Each 13.5 mg extended-release capsule has a Swedish orange cap with (b) (4) printed on it and a white body; each 13.5 mg capsule contains the equivalent of 15 mg oxycodone HCl • Each 18 mg extended-release capsule has a rich yellow cap with (b) (4) printed on it and a white body; each 18 mg capsule contains the equivalent of 20 mg oxycodone HCl • Each 27 mg extended-release capsule has a light gray cap with (b) (4) printed on it and a white body; each 27 mg capsule contains the equivalent of 30 mg oxycodone HCl • Each 36 mg extended-release capsule has a flesh cap with (b) (4) printed on it and a white body; each 36 mg capsule contains the equivalent of 40 mg oxycodone HCl	Acceptable

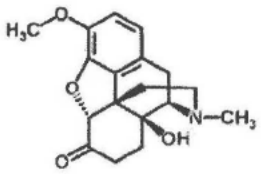
Conclusion: Acceptable.

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

Start of Sponsor Material

(b) (4)

(b) (4) The structural formula for oxycodone (b) (4) is as follows:



$C_{18}H_{21}NO_4$ MW 315.37 g/mol

The chemical name is 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one.

Oxycodone base is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone is present as myristate salt in the (b) (4) formulation.

Each (b) (4) capsule contains either 9, 13.5, 18, 27, or 36 mg of oxycodone (equivalent to 10, 15, 20, 30, or 40 mg of oxycodone HCl, respectively) and the following inactive ingredients: myristic acid, yellow beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide. The capsule shells collectively contain titanium dioxide, (b) (4) hypromellose, and water.

End of Sponsor Material

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: XTAMPZA ER Established Name: Oxycodone extended-release capsule	Acceptable. Note that the final proprietary name has not been updated yet in the package insert Acceptable
Dosage form and route of administration	Dosage form: Capsule Route of administration: Oral	Acceptable Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	9 mg, 13.5 mg, 18 mg, 27 mg and 36 mg oxycodone (base) equivalent to 10 mg, 15 mg, 20 mg, 30 mg and 40 mg oxycodone HCl	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Myristic acid, yellow beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide. The capsule shells collectively contain titanium dioxide, (b) (4) hypromellose, and water.	Acceptable
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Opioid analgesic	Acceptable
Chemical name, structural formula, molecular weight	4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one $C_{18}H_{21}NO_4$ 315.37 g/mol	Acceptable Acceptable Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	N/A

Conclusion: Acceptable

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

Start of Sponsor Material

OXYCODONE DETERx capsules are supplied in 100-count bottles with a child-resistant closure as presented in Table 7:

Table 7: Summary of Oxycodone DETERx Capsule Strengths

Strength	Capsule Color	Capsule Text	NDC Number
9 mg (equivalent to 10 mg oxycodone HCl)	ivory cap/white body	(b) (4)	NDC 24510-110-10
13.5 mg (equivalent to 15 mg oxycodone HCl)	Swedish orange cap/white body		NDC 24510-115-10
18 mg (equivalent to 20 mg oxycodone HCl)	rich yellow cap/white body		NDC 24510-120-10
27 mg (equivalent to 30 mg oxycodone HCl)	light gray cap/white body		NDC 24510-130-10
36 mg (equivalent to 40 mg oxycodone HCl)	flesh cap/white body		NDC 24510-140-10

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F)

End of Sponsor Material

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	9 mg, 13.5 mg, 18 mg, 27 mg and 36 mg oxycodone (base) equivalent to 10 mg, 15 mg, 20 mg, 30 mg and 40 mg oxycodone HCl	Acceptable
Available units (e.g., bottles of 100 tablets)	100 tablets/bottle	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See reproduced text above	Acceptable
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).	Acceptable

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	None.	Information request to be sent.

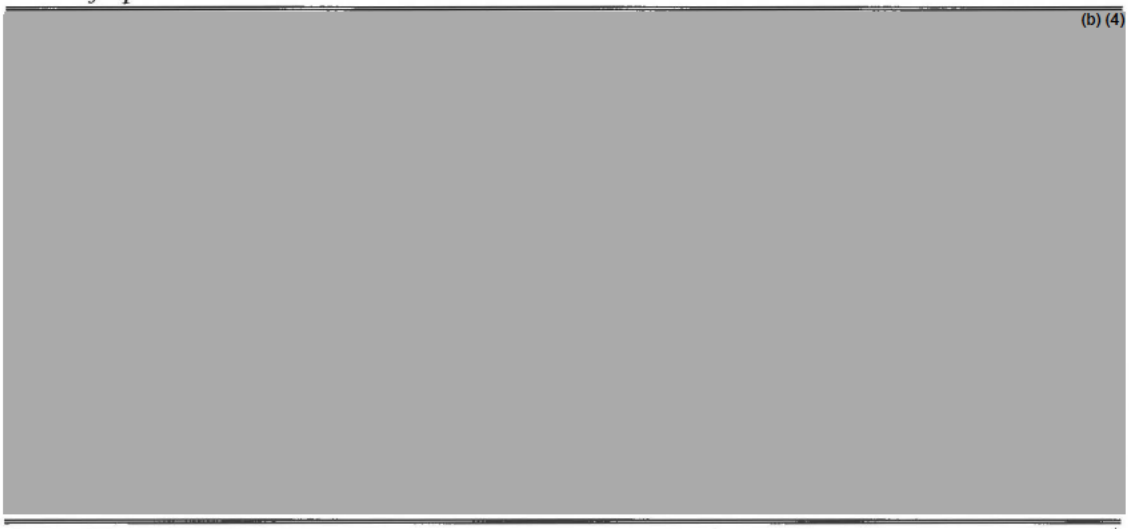
Conclusion: Pending issue resolution.

1. Labels

1) Immediate Container Label

Start of Sponsor Material

(b) (4)



End of Sponsor Material

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Xtampza Oxycodone	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	9 mg, 13.5 mg, 18 mg, 27 mg and 36 mg oxycodone (base) equivalent to 10 mg, 15 mg, 20 mg, 30 mg and 40 mg oxycodone HCl	Acceptable
Net contents (21 CFR 201.51(a))	100 capsules	Acceptable
Lot number per 21 CFR 201.18	Yes	Acceptable
Expiration date per 21 CFR 201.17	Yes	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	Acceptable
Storage (not required)	Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F)	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	9 mg: NDC 24510-110-10 13.5 mg: NDC 24510-115-10 18 mg: NDC 24510-120-10 27 mg: NDC 24510-130-10 36 mg: NDC 24510-140-10	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Yes	Acceptable
Name of manufacturer/distributor	Collegium Pharmaceutical, Inc. Canton, MA 02021	Acceptable
Others	N/A	N/A

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Pending.
Revise the bottle labels and various locations in the package insert such that the current drug product name (b) (4) reads as "(oxycodone) extended-release capsules". Only the established name should be included in the parenthesis.

2) Cartons
N/A.

ASSESSMENT OF THE BIOPHARMACUETICS

Introduction:

Collegium Pharmaceutical, Inc. is submitting Oxycodone DETERx®, an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone (base). The hydrochloride salt of this agent has been used medically since 1917 and thus has an extensive clinical history. The formulation provides analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Currently, there is an extended release (ER) tablet of oxycodone on the market (OxyContin® [oxycodone hydrochloride extended-release tablets] (approved by the FDA on 2014, Stamford, CT, Purdue Pharma L.P.), which contains a relatively large dose of drug and is attractive to abusers as the time-release mechanism can be defeated by relatively simple manipulations including chewing or crushing the tablet. Oxycodone DETERx® has been developed to address these and other limitations of currently marketed ER opioid products.

BCS Classification:

According to the Applicant, Oxycodone Base is classified as a Biopharmaceutical Classification System (BCS) Class III compound (High solubility/low permeability).

The pH solubility profile is presented in **Biopharm Table 1**.

Biopharm Table 1. Solubility of Purified Oxycodone Base in Aqueous Solution as a Function of pH

Measured pH	Experimental Solubility (mg/mL)	Experimental Solubility (M)	Calculated Solubility (M)
(b) (4)			

(b) (4)

Drug Product:

Oxycodone DETERx®, is an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone (base). It is intended for dosing every 12 hours. The microspheres are comprised (b) (4) of oxycodone base (API): (b) (4) The microspheres are formed (b) (4) and encapsulated to produce capsules that contain oxycodone in an amount equivalent to 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg oxycodone HCl.

(b) (4)

The composition is shown in the following **Biopharm Table 2**:

Biopharm Table 2 : Statement of Composition

Component	Reference to Quality Standard	Function	Dose Strength (Oxycodone Hydrochloride Equivalent)				
			40 mg	30 mg	20 mg	15 mg	10 mg
			Quantity per Capsule (mg)				
							(b) (4)
Oxycodone Base	In-house standard	Drug Substance					
Myristic Acid	FG/NF						
Yellow Beeswax	NF						
Carnauba Wax	NF						
Stearoyl polyoxyl-32 glycerides	NF						
							(b) (4)
Magnesium Stearate	NF						
Colloidal Silicon Dioxide	NF						
							(b) (4)
							(b) (4)
Hypromellose Capsule Shell							
							(b) (4)

According to the Applicant, sprinkling capsule contents on several soft foods prior to in vitro dissolution does not impact the in vitro dissolution profile relative to intact capsules. Passing capsule contents through enteral tubes of various dimensions (simulating NG or G tubes) with the aid of various liquid vehicles does not impact the in vitro dissolution profile relative to intact

capsules. Also, the Applicant stated that opening the capsules and crushing or chewing prior to fed state administration did not significantly affect PK (to be qualified by the OCP review team).

Risk Assessment:

Initial Biopharmaceutics Assessment of Risk based on Drug Product Dissolution Testing

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	FACTORS AFFECTING THE CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
In vitro dissolution	Change in dissolution mechanism and kinetics; drug substance particle size	4	3	4	**48**	Based on the Risk Assessment and development work, it seems that the particle size will affect to dissolution CQA. There batch to batch variability in dissolution that can potentially impact safety and efficacy will be a review issue.
Alcohol dose dumping	Dose dumping due to enhanced solubility of rate controlling excipients and drug in alcohol	4	4	3	**48**	Although no in vitro dose dumping was observed under the condition tested, this needs to be confirmed after reviewing in vivo data from alcohol dose dumping study.

RPN < 25 is considered **low** risk; RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.

After review, the risk assessment is revised as shown in the following table

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	FACTORS AFFECTING THE CQA	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
In vitro dissolution	Change in dissolution mechanism and kinetics; drug substance particle size	4	3	3	**36**	Based on the Risk Assessment and development work, it seems that the particle size will affect to dissolution CQA. However, a discriminatory dissolution method has been developed, decrease the difficulties of detectability.
Alcohol dose dumping	Dose dumping due to enhanced solubility of rate controlling excipients and drug in alcohol	1	4	3	12	There is no dose dumping detected in the in vitro dose dumping study under the condition tested.In vivo alcohol dose dumping study data confirmed that there is no dose dumping issues.

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

33A. DISSOLUTION METHOD

The following dissolution method and dissolution acceptance criterion were found acceptable and agreed upon with the Applicant (refer to Responses to IR dated August 3rd, 2015) for the proposed drug product (10 mg, 15 mg, 20 mg, 30 mg, or 40 mg) for the release and stability test.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
I	100 rpm	900 mL	37°C	USP Sodium Acetate buffer at pH 4.5 with 0.03% Tween 20	Drug amount dissolved (b) (4)% at 1h (b) (4)% at 4h NLT (b) (4)% at 12h

33A.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The dissolution method was evaluated to determine the effect varying dissolution parameters would have on the *in vitro* drug release (for more details refer to dissolution method report under \\cdsesub1\evsprod\nda208090\0000\m3\32-body-data\32p-drug-prod\oxycodone-deterx-hard-shell-capsule\32p2-pharm-dev\col-003-12-005-r-02-dissolution-developm.pdf). The following method parameters were evaluated:

- Dissolution apparatus and rotation speed,
- The effect of media type,
- Effect of pH and Buffer,
- Surfactant type/concentration,

Dissolution apparatus and rotation speed

Baskets were elected over paddles based on the following considerations:

(b) (4)

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33B. DISSOLUTION ACCEPTANCE CRITERION

The setting of the dissolution acceptance criterion was based on the mean dissolution profiles of pivotal clinical batches (for 40 mg) and registration batches (for 10 mg, 15 mg, 20 mg, 30 mg strength). The original proposed dissolution method and acceptance criterion is shown as follows.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
I	100 rpm	900 mL	37°C	USP Sodium Acetate buffer at pH 4.5 with 0.03% Tween 20	Drug amount dissolved (b) (4)% at 1h (b) (4)% at 4h NLT (b) (4)% at (b) (4)h

33B.1 What data are available to support the proposed dissolution acceptance criterion?

Dissolution data collected using the QC method (pH 4.5, sodium acetate buffer supplemented with 0.03% Tween-20 using USP Apparatus I [baskets] at 100 RPM) by dose, and batch at product release for batches used in clinical trials are provided in **Biopharm Table 10.**

Biopharm Table 10. Dissolution Rates Across Batches Used in Clinical Trials

Apparatus/RPM	Baskets / 100 RPM	Medium /Volume	pH 4.5 Acetate Buffer with 0.03% Tween 20/ 900 mL
	% Dissolved (% D)	Time Points (hr)	
	Range (%)	(b) (4)	
Clinical Trial Batch			
10 mg (CP-OXYDET-08) (Lot # 3100343R)	% D		
	Range (%)		
20 mg (CP-OXYDET-08) (Lot # 3100344R)	% D		
	Range (%)		
40 mg (CP-OXYDET-15, -18, -17, -19, -21, -24, -25, -08) (Lot # 3100363R)	% D		
	Range (%)		
Registration Batch #1			
10 mg (CP-OXYDET-08) (Lot # 3104073R)	% D		
	Range (%)		
20 mg (CP-OXYDET-08) (Lot # 3104079R)	% D		
	Range (%)		

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33B.2 Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

The initially proposed acceptance criterion was not acceptable and during the review cycle the Applicant was requested to tighten the dissolution acceptance criteria. Specifically, the following comment was conveyed to the Applicant in the filing communication:

"There is no IVIVC approved for your proposed product. Therefore, the selection of the dissolution acceptance criteria limits should be based on the mean target (biobatches) value± (b) (4) % variation and NLT (b) (4) % for the last specification time-point. Implement these acceptance criteria for your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test. Also, provide justification for the selected last specification time point (i.e., (b) (4) hrs) when more than (b) (4) % of the drug is released within 12 hours"

On April 6, 2015, COLLEGIUM Pharmaceutical submitted Responses for the justification of the dissolution acceptance criteria to NDA # 208090 and proposed new commercial dissolution acceptance criteria for Oxycodone DETERx capsule (all strengths) shown as follows

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
I	100 rpm	900 mL	37°C	USP Sodium Acetate buffer at pH 4.5 with 0.03% Tween 20	Drug amount dissolved (b) (4) % at 1h (b) (4) % at 4h NLT (b) (4) % at (b) (4) h

The Applicant agreed with the Agency [redacted] (b) (4)

The applicant thus proposed maintain the original proposed specification of NLT [redacted] (b) (4)% at [redacted] (b) (4) hours [redacted] (b) (4)

Reviewer's Assessment:

- After reviewing the data included in the responses dated April 6, 2015, the agency believed that as a result of a 12 hour specification of NLT [redacted] (b) (4)%, the rate [redacted] (b) (4) is reasonable. Thus, the Agency recommended that NLT [redacted] (b) (4)% at 12 hour should be included in the acceptance criteria. Another IR was sent to the applicant on July 24, 2015. In the response dated August 3rd, 2015, the Applicant accepted the dissolution acceptance criteria the Agecy recommended for Oxycodone DETERx (10 mg, 15 mg, 20 mg, 30 mg, and 40 mg).

- The Applicant provided sufficient data showing discriminating ability supporting the following dissolution method and acceptance criteria for Oxycodone DETERx capsule (10 mg, 15 mg, 20 mg, 30 mg, or 40 mg).

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
I	100 rpm	900 mL	37°C	USP Sodium Acetate buffer at pH 4.5 with 0.03% Tween 20	Drug amount dissolved [redacted] (b) (4)% at 1h [redacted] (b) (4)% at 4h NLT [redacted] (b) (4)% at 12h

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

34 A. FORMULATION

Drug products used in clinical studies and registration batches are identical to the commercial formulation, differing only in the capsule color and printing ink level.

34 B. MANUFACTURING PROCESS

The Applicant proposed the following changes for the commercial scale manufacturing process:

[redacted] (b) (4)

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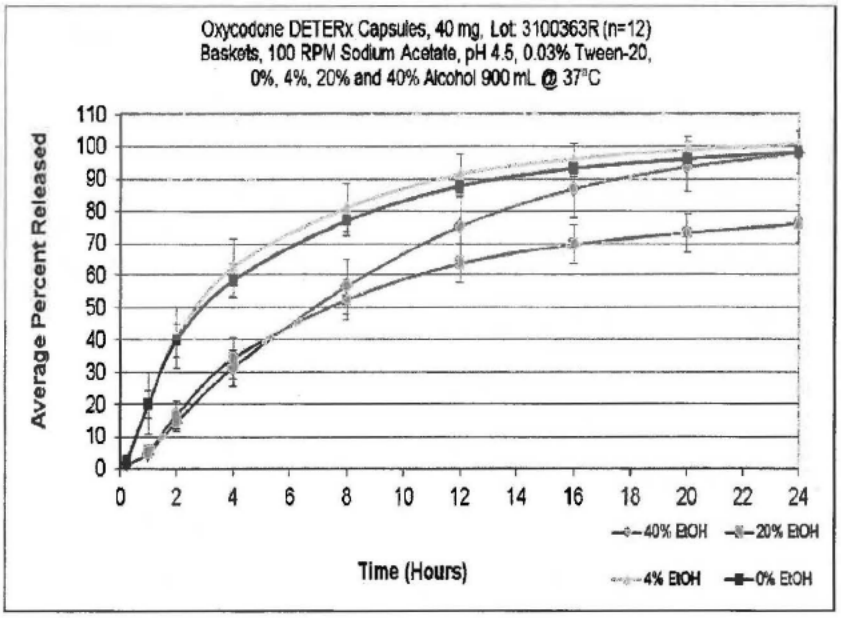
Reviewer's Assessment:

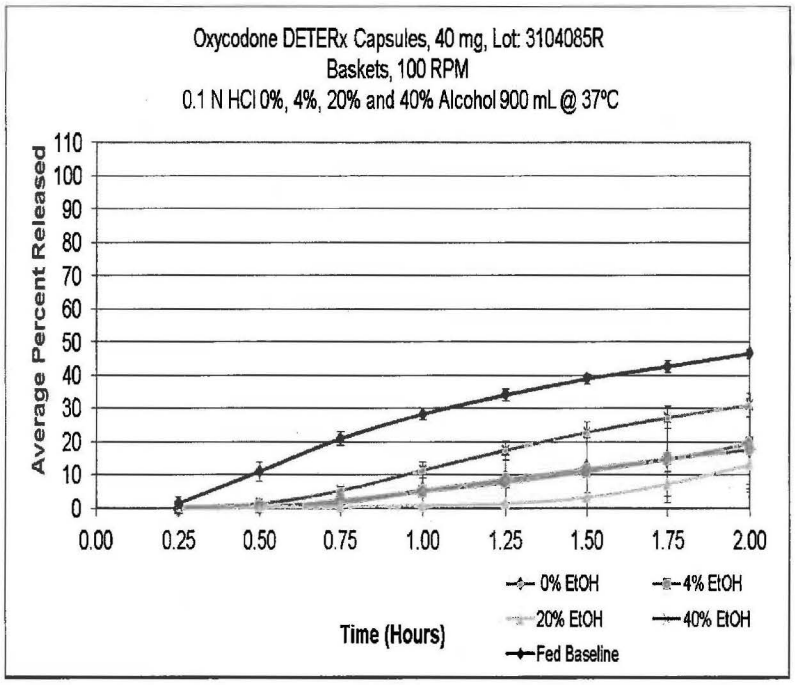
(b) (4)

34 D. ALCOHOL DOSE DUMPING

In the submission, dissolution studies (40 mg Capsule Strength) using Baskets method, 100 rpm Sodium Acetate, pH 4.5, 0.03% Tween 20 Media with 0%, 4%, 20% and 40% Ethanol through 24 Hours were performed, dissolution of DETERx at 40%, 20%, and 4% ethanol were found to be equivalent to or slower than that for 0% ethanol (**Biopharm Figure 13**), suggesting that the presence of alcohol will not cause dose dumping. According to the Applicant, in vivo study confirmed these results (details could be found in clinical pharmacology review). Dissolution Profiles (40 mg Capsule Strength) in Medium (0.1N HCl) with 0%, 4%, 20% and 40% Ethanol through 2 Hours Compared with Fed Baseline was shown in **Biopharm Figure 14**.



Biopharm Figure 13 Dissolution Profiles (40 mg Capsule Strength) in Fed Media (pH 4.5 sodium acetate buffer supplemented with 0.03% Tween 20) with 0%, 4%, 20% and 40% Ethanol through 24 Hours



Biopharm Figure 14 Dissolution Profiles (40 mg Capsule Strength) in Fasted Media (0.1N HCl) with 0%, 4%, 20% and 40% Ethanol through 2 Hours Compared with Fed Baseline

Reviewer's Assessment:

The dissolutions of DETERx in pH 4.5 medium in the presence of 40%, 20%, and 4% ethanol were found to be equivalent to or slower than that in 0% ethanol. However, in the medium of 0.1 N HCl, dissolution of DETERx in the presence of 40% ethanol was found to be faster than that in 0% ethanol.

An in vivo study confirms that there is no alcohol dose dumping potential.

Based on the in vitro and in vivo data, presence of alcohol will not cause dose dumping when Oxycodone DETERx is taken with food.

34 E. ABUSE DETERRENT CHARACTERISTICS

34E.1. Is there any dissolution data available to support the abuse deterrent characteristics of the proposed product?

Manipulation studies

Biopharm Table 21: Summary of physical manipulation studies

Experiment Report Number	Objective	Tested parameters/solvents	Method of Evaluation	Comparator product (s)
Particle size reduction (PSR) studies with household tools COL-003-12-002-R	To evaluate various means to reduce the particle size (increase the surface area) and increase drug release from the Oxycodone DETERx capsule contents (microspheres)	PSR with 11 utensils that crush, grind, grate and chop: (1) coffee grinder, (2) pepper mill, (3) microplane fine grater, (4) tablet crusher (with teeth), (5) tablet crusher (with teeth and modified to increase product contact), (6) mortar and pestle, (7) rotating chopper, (8) herb mill, (9) pill splitter, (10) hammer, and (11) garlic press	Particle Size Analysis and Dissolution	OxyContin OP
Mortar and pestle optimization study CO-003-13-003-R	To test the impact of mortar & pestle type, number of capsules crushed, grinding frequency, and grinding time on drug release	PSR with 3 types of mortar & pestle types (ceramic, stone, glass). Most effective mortar & pestle type (ceramic) was then used to evaluate the optimal combination of grinding time (1, 2, 4, and 6 minutes), quantity of capsules (contents of 1, 3, or 5 capsules), and grinding frequency (100 or 200 RPM) on drug release.	Dissolution	None
Independent verification of PSR COL-003-13-006-R	To compare results from PSR techniques tested at Collegium with results obtained from an independent lab (Boston Analytical)	PSR with 3 most effective utensils identified in Collegium study	Dissolution	OxyContin OP
Heat and Freeze PSR studies COL-003-13-005-R	To evaluate Oxycodone DETERx particle size and drug release after freezing or heating of microspheres followed by tampering with the three most successful PSR techniques	Control, frozen, and heated samples crushed with 3 most successful PSR techniques	Particle Size Analysis and Dissolution	None

PSR = particle size reduction; RPM = revolutions per minute.

Biopharm Table 22: Particle Size Reduction Results (Laser Diffraction)

Tool	D10		D50		D90	
	Microns	% from Control	Microns	% from Control	Microns	% from Control
Control	**176**	-	**320**	-	**598**	-
Coffee Grinder	164	93.2	307	95.9	580	97.0
Pepper Mill	165	93.8	303	94.7	545	91.1
Fine Grater	Not Performed					
Tablet Crusher	Not Performed					
Tablet Crusher (modified)	185	105.1	330	103.1	611	102.2
Mortar and Pestle (glass)	139	79.0	263	82.2	415	69.4
Food Chopper	159	90.3	295	92.2	547	91.5
Herb Mill	Not Performed					
Pill Splitter	Not Performed					
Hammer	133	75.6	279	87.2	512	85.6
Garlic Press	Not Performed					

Not Performed = Quantitative analysis was not performed if it was not feasible to apply the tool to the Oxycodone DETERx microspheres (i.e., there was no product contact between tool and microspheres)

Reviewer's Assessment:

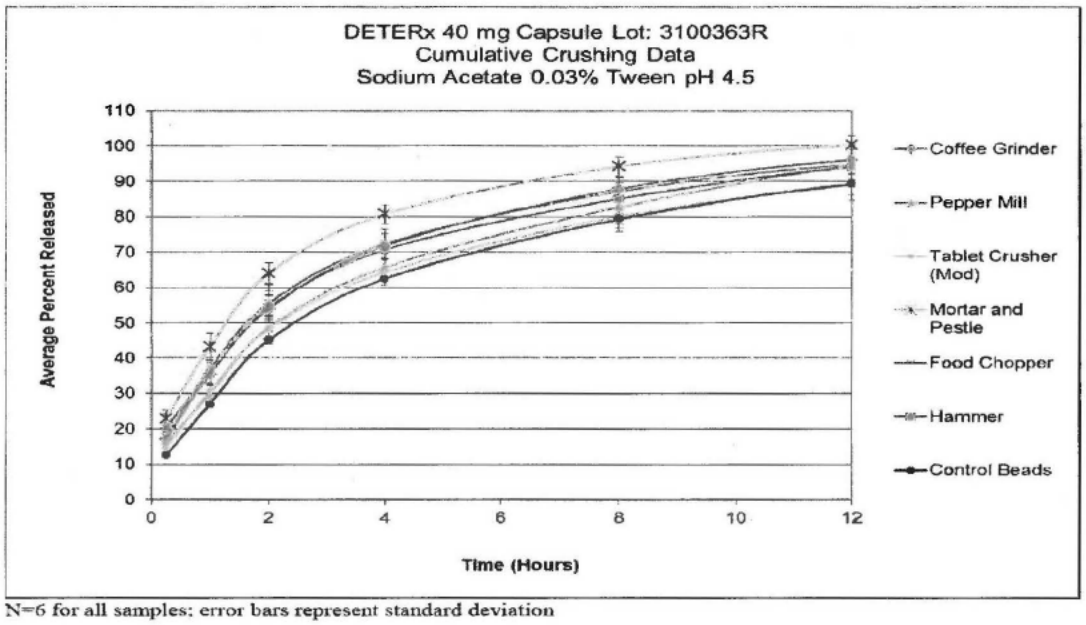
According to **Biopharm Table 21** and **Table 22**, mortar and pestle method is the most efficient method to reduce particle size.

Dissolution studies

USP Apparatus II (paddles) at 50 RPM was utilized for both products as paddles allowed for introduction of crushed powder into the dissolution vessels. The validated QC media (sodium acetate buffer pH 4.5 supplemented with 0.03% Tween 20) was used for Oxycodone DETERx

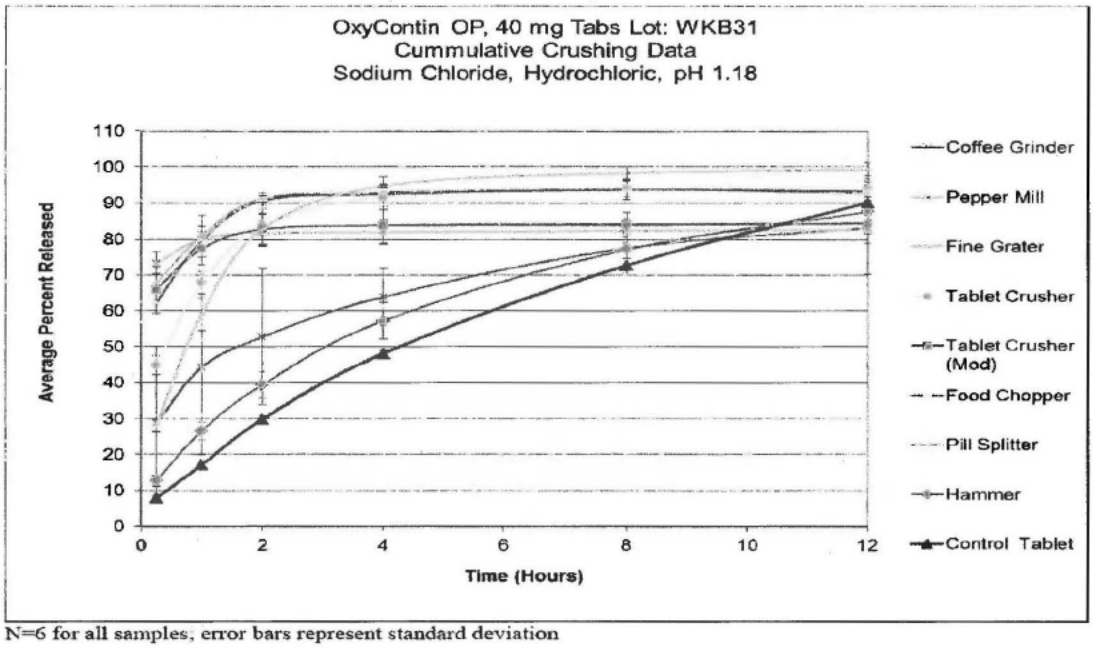
and the USP specified dissolution media (Simulated Gastric Fluid without enzymes) was used for OxyContin OP.

Dissolution Results Summary for DETERx 40 mg Capsules and OxyContin OP 40 mg Tablets after PSR Compared with Control (intact beads) was shown in the following two figures



N=6 for all samples; error bars represent standard deviation

Biopharm Figure 15. Dissolution Results Summary for DETERx 40 mg Capsules and OxyContin OP 40 mg Tablets after PSR Compared with Control (intact beads)



N=6 for all samples; error bars represent standard deviation

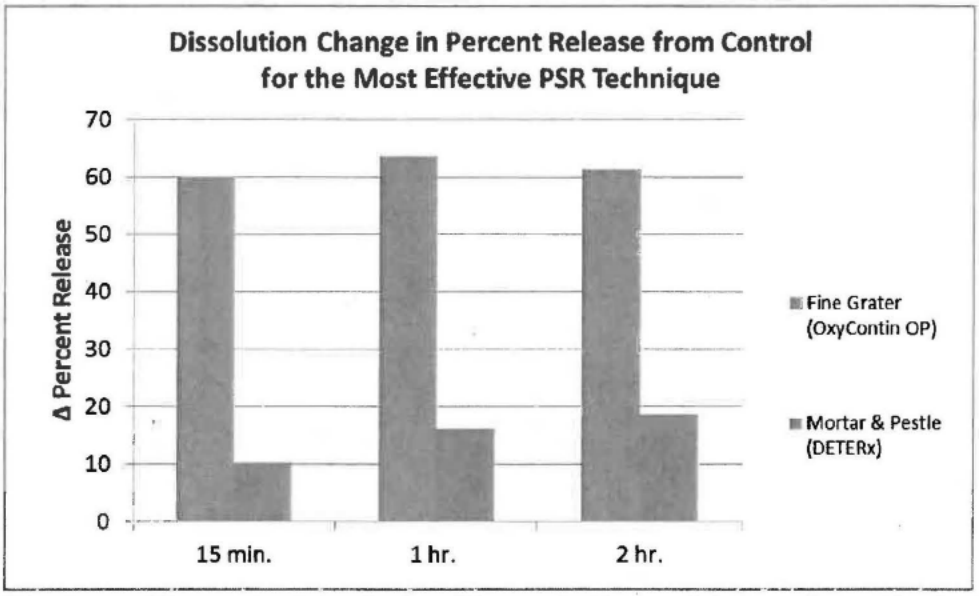
Biopharm Figure 16. Dissolution Results Summary for OxyContin OP 40 mg Tablets after PSR Compared with Control

For Oxycodone DETERx, The most effective PSR method was crushing with a mortar & pestle. All methods that resulted in PSR produced a dissolution difference of <20% compared with control at all time points through 12 hours of dissolution, including early time points (up to two hours).

For OxyContin OP tablets, The pepper mill, fine grater, modified tablet crusher, and food chopper all produced a dissolution difference of >54% compared to intact tablets at the 15 minute time point of dissolution.

According to the applicant, using the most effective methods, the changes in dissolution when compared to the control (intact release profile) for OxyContin OP were considerably higher than those observed for Oxycodone DETERx.

The results are shown in **Biopharm Figure 17.**:



Biopharm Figure 17. Dissolution Change in Percent Release from Control for the Most Effective PSR Technique

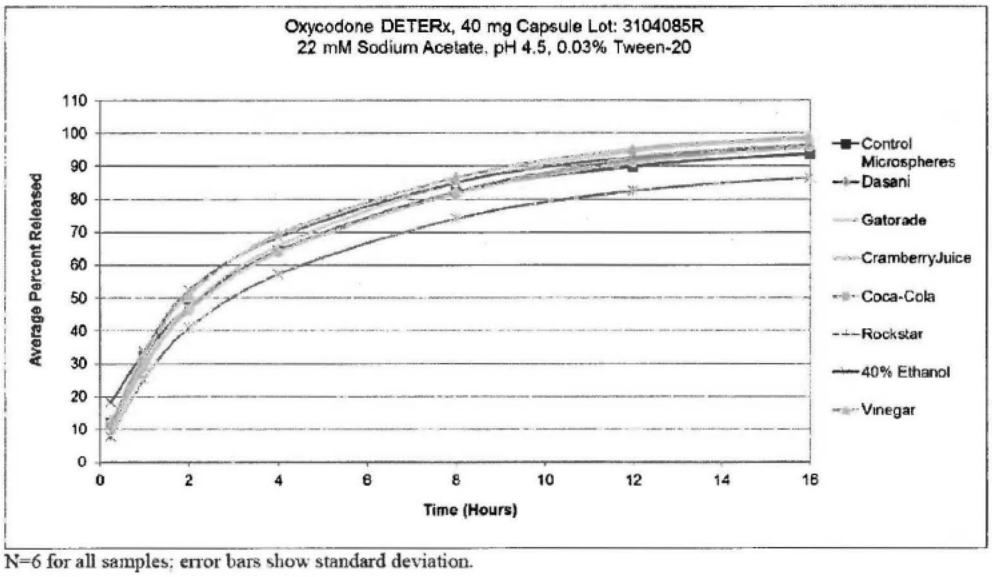
Pretreatment by freezing and heating did not enhance the effectiveness of PSR tools applied to capsule contents (Page 167 of 32p22-drug-product-crushed_intact).

Reviewer's Assessment:

Based on the results provided by the applicant on **Dissolution Studies comparing crushed and intact product,** this reviewer agrees that using the most effective methods tested, the changes in dissolution when compared to the control (intact release profile) for OxyContin OP were considerably higher than those observed for Oxycodone DETERx. Oxycodone DETERx shows abuse deterrent property compared to OxyContin OP ER product.

Dissolution/extraction studies of DETERx Capsule soaking in beverages or being mixed with soft food

Dissolution test was performed after soaking the contents of Oxycodone DETERx Capsule Contents for 10 minutes in all the beverages tested. The results are shown in **Biopharm Figure 18**. Dissolution profiles comparison was performed following mixing the contents of Oxycodone DETERx Capsule or whole capsule with soft food for up to 60 minutes and the results are shown in **Biopharm Table 23**.



N=6 for all samples; error bars show standard deviation.

Biopharm Figure 18. Dissolution of Oxycodone DETERx Capsule Contents Following Short Duration Soaking in Beverages

Biopharm Table 23. Summary of f2 Similarity Factors for Dissolution Following Mixing with Soft Foods Compared to Whole Capsules

Soft Food	f2 Similarity Factors		
	T = 0 min	T = 30 min	T = 60 min
Yogurt	77	74	72
Vanilla Pudding	73	69	65
Vanilla Ice Cream	65	68	71
Applesauce	76	80	77
Strawberry Jam	73	70	73

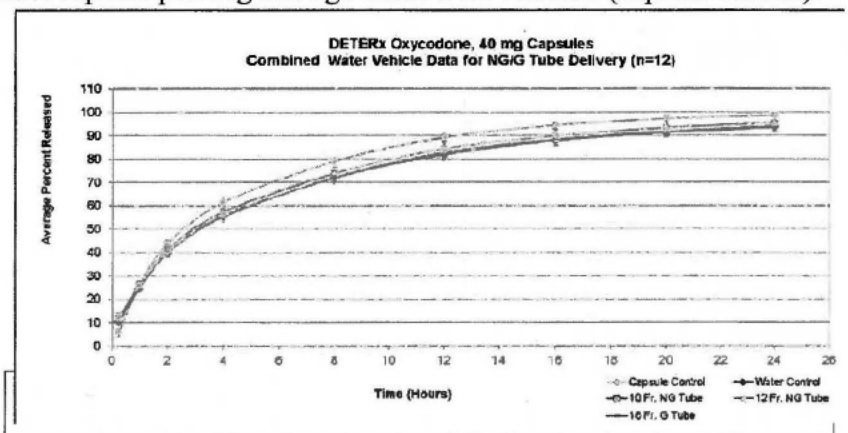
According to the Applicant, the Oxycodone DETERx microspheres retained their ER characteristics after soaking for 10 minutes in all beverages tested. And for all 5 soft foods

tested, no significant impact on dissolution was observed after mixing microspheres with various soft foods and holding them at room temperature for up to 60 minutes (**Table 23**).

Dissolution following G/NG Tube Passage

In addition to providing tamper resistant properties, the DETERx formulation offers the potential benefit of administration via alternative routes to the patients with swallowing difficulties. These alternative oral routes of administration include administration via a feeding tubes such nasogastric (NG) or gastrostomy (G) tubes. *In vitro* dissolution was conducted after the delivery of capsule contents (microspheres) through NG/G tubes using 5 different liquid vehicles (water, Jevity, ensure, 2% milk, whole milk) to assist the transfer. Dissolution was conducted using standard USP Apparatus I (Basket) dissolution apparatus with 22 mM Sodium Acetate buffer pH 4.5 plus 0.03% Tween 20 as the dissolution media per the dissolution method in CP003FP-A. Before the start of dissolution testing, a volume of 15 mL of vehicle was used to initially pass microspheres through the tube followed by rinsing with 45 mL of water for a total volume of 60 mL being used to deliver the microspheres to the dissolution basket.

The dissolution test demonstrated that the dissolution characteristics of the capsule contents were not altered as all f2 values were greater than 50 when compared to dissolution of microspheres (without passing through tubes but using DETERx microspheres with various vehicles added to the dissolution medium) or with intact capsule dissolution results. A representative figure (**Biopharm Figure 19**) shows the similarity of dissolution profiles between microspheres passing through tubes with vehicles and without passing through tubes (water control). It also shows the similarity between dissolution profiles of microspheres passing through tubes with vehicles and intact capsule passing through tubes with vehicles (capsule control).



Timepoint (Hours)	0.25	1	2	4	8	12	16	20	24	f2 (Water control)	f2 (Capsule control)
Water Control	11	24	40	55	72	82	88	91	94	NA	NA
Control Capsule	6	25	44	61	79	89	94	97	99	NA	NA
10 Fr. NG Water	12	26	41	57	74	84	90	94	95	84	68
12 Fr. NG Water	12	26	41	56	74	84	90	93	95	86	66
16 Fr. G Water	12	26	40	56	72	83	88	92	94	93	63

Biopharm Figure 19. Graph of NG/G Tube Results using Water as the Vehicle

Reviewer's Assessment:

Based on the results provided by the applicant on **Short-duration Soaking Study, Soft-food Dissolution Study, G/NG Tube Passage Study,** this reviewer agrees that no significant impact on dissolution was observed after soaking for 10 minutes in all tested beverages or after mixing microspheres with soft foods. No significant impact on dissolution after passing the capsule contents (microspheres) through NG/G tubes using 5 different liquid vehicles (water, Jevity, ensure, 2% milk, whole milk).

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

ONDP/Division of Biopharmaceutics had reviewed NDA 208090 for oxycodone. The dissolution method is adequate and the Agency recommended dissolution acceptance criteria were adopted by the applicant. (b) (4) The alcohol dose dumping potential is minimal when Oxycodone DETERx is taken with food.

From the Biopharmaceutics perspective, NDA 208090 for Oxycodone DETERx is recommended for **APPROVAL**.

Fang Wu, Ph.D.
Primary Biopharmaceutics Reviewer
OPQ/ONDP/DBP

John Duan, Ph.D.
Secondary Biopharmaceutics Reviewer
&Branch Chief
OPQ/ONDP/DBP

cc Sandra Suarez and Paul Seo

Supervisor Comments and Concurrence: **Concur. John Duan**

QUALITY ASSESSMENT

Recommendation:
NDA: Approval /Complete Response

NDA 208090
Review # 1
Review Date 5/10/2015

Drug Name/Dosage Form	Oxycodone DETERx, Extended release Capsules
Strength	10mg, 15mg, 20mg, 30mg and 40mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Collegium Pharmaceutical, Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Process	Tarun Mehta	VI/2
Microbiology	Tarun Mehta	VI/2
Facility	Robert Wittorf	II/5

Table of Contents

32 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

35. Is a Comparability Protocol included in the application for manufacturing process or manufacturing site post approval changes? If so, what post-approval changes are specified? What is the method of evaluation of the changes and the acceptance criteria for the change?? How will the changes be reported?

Reviewer's Assessment: Adequate

There is no post approval changes proposed in the NDA. For the commercial production the applicant propose to use (b) (4) for the registration batches. There are few changes proposed (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature:

The applicant has instituted an adequate strategy in developing the manufacturing process. The bench and pilot scale process development were used to evaluate the each unit operation. Prior to the process development study of the pilot scale batches; the applicant highlighted the initial risks involved in each unit operation (b) (4) After studding these risks the development was performed (b) (4) The important aspects of the process were (b) (4) Using the developed process, the applicant has successfully manufactured the drug product at (b) (4) kg scale. To study the technology transferred of pilot scale to commercial scale manufacturing the applicant has manufactured one placebo batch.

Supervisor Comments and Concurrence:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208090	**Submission Type: 505b(2)**	**Established/Proper Name: Xtampza ER – Oxycodone extended relaease capsules**
Applicant: Collegium Pharmaceuticals, Inc.	**Letter Date: 12/12/2014**	**Dosage Form: Capsules**
Chemical Type: Non-NME	**Stamp Date: 12/12/2014**	**Strength: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg (HCl salt)**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		CMC: Fileable Biopharmaceutics: Fileable
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			See 74 day letter comments for CMC on page 11. See 74 day letter comments for biopharmaceutics on page 12.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	x	
2.	Botanical[1]	☐	x	
3.	Naturally-derived Product	☐	x	
4.	Narrow Therapeutic Index Drug	☐	x	
5.	PET Drug	☐	x	
6.	PEPFAR Drug	☐	x	
7.	Sterile Drug Product	☐	x	
8.	Transdermal[1]	☐	x	
9.	Pediatric form/dose[1]	☐	x	
10.	Locally acting drug[1]	☐	x	
11.	Lyophilized product[1]	☐	x	
12.	First generic[1]	☐	x	
13.	Solid dispersion product[1]	☐	x	
14.	Oral disintegrating tablet[1]	☐	x	
15.	Modified release product[1]	x	☐	Extended release drug
16.	Liposome product[1]	☐	x	
17.	Biosimiliar product[1]	☐	x	
18.	Combination Product	☐	x	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
19.	Other	☐	x	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Regulatory Considerations					
20.	USAN Name Assigned		x	☐	
21.	End of Phase II/Pre-NDA Agreements		x	☐	
22.	SPOTS (Special Products On-line Tracking System)		☐	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	x	
24.	Comparability Protocol(s)[2]		☐	x	
25.	Other		☐	x	
Quality Considerations					
26.	Drug Substance Overage		☐	x	
27.	Design Space	Formulation	☐	x	
28.		Process	☐	x	
29.		Analytical Methods	☐	x	
30.		Other	☐	x	
31.	Real Time Release Testing (RTRT)		☐	x	
32.	Parametric Release in lieu of Sterility Testing		☐	x	
33.	Alternative Microbiological Test Methods		☐	x	
34.	Process Analytical Technology[1]		☐	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	x	
36.		Excipients	☐	x	
37.		Microbial	☐	x	
38.	Unique analytical methodology[1]		☐	x	
39.	Excipients of Human or Animal Origin		☐	x	
40.	Novel Excipients		x	☐	Myristic acid, yellow beeswax, carnauba wax, and hypromellose are novel excipients (b) (4) (b) (4)
41.	Nanomaterials[1]		☐	x	
42.	Hold Times Exceeding 30 Days		☐	x	
43.	Genotoxic Impurities or Structural Alerts		x	☐	(b) (4) is a degredant
44.	Continuous Manufacturing		☐	x	
45.	Other unique manufacturing process[1]		☐	x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	
47.	New delivery system or dosage form[1]		☐	x	
48.	Novel BE study designs		☐	☐	
49.	New product design[1]		☐	x	
50.	Other		☐	x	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	x	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a	x	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols				
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ 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	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x	☐	☐	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	x	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients	x	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS

	❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				
8.	Does the application contain dissolution data? • Is the dissolution test part of the DP specifications? • Does the application contain the dissolution method development report including data supporting the discriminating ability?	x	☐	☐	• The proposed dissolution method is as follows: Parameter: Selection Apparatus: USPI(Baskets) Agitation Speed: 100RPM pH: 4.5 Buffer: USP Sodium Acetate Surfactant: Tween 20 Surfactant Level: 0.03% Volume: 900mL Temperature: 37 °C The link is as follows: \\CDSESUB1\evsprod\NDA208090\208090.enx. Page 48 of col-003-12-005-r-02 Dissolution Development Report in 3.2.P.2 Pharmaceutical Development • Drug release acceptance criterion

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
					<table><tr><td>Time (hrs)</td><td>Amount Dissolved</td></tr><tr><td>1</td><td>(b) (4)%</td></tr><tr><td>4</td><td>(b) (4)%</td></tr><tr><td>(b) (4)</td><td>NLT (b) (4)%</td></tr></table> The link is as follows: \\CDSESUB1\evsprod\NDA208090\208090.enx. Page 2 in 3.2.P.5.1 specifications • The application contains the dissolution method development report including data supporting the discriminating ability. The link is as follows: \\CDSESUB1\evsprod\NDA208090\208090.enx. Page 34 of col-003-12-005-r-02 Dissolution Development Report in 3.2.P.2 Pharmaceutical Development
9.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	x	☐	☐	When taken with food under single- or multiple-dose administration, Oxycodone DETERx treatment results in oxycodone exposures similar to and/or bioequivalent (BE) with those achieved by OxyContin OP (study CP-OXYDET-15: single-dose relative bioavailability and food effect study comparing the proposed product to the reference) \\CDSESUB1\evsprod\NDA208090\208090.enx. Page 8 of 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods This study will be reviewed by Clinical Pharmacology review team.
10.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	x	☐	☐	Drug products used in clinical studies and registration batches are identical to the commercial formulation, differing only in the capsule color and printing ink level. \\CDSESUB1\evsprod\NDA208090\208090.enx. Page 8 of 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
11.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	x	☐	☐	(b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
					(b) (4) Page 8 of 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
12.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	x	☐	☐	Varying strengths of Oxycodone DETERx capsules (10, 15, 20, 30, and 40 mg) were tested with different concentrations of ethyl alcohol (0%, 4%, 20%, 40%) in media simulating both fed (pH 4.5 sodium acetate buffer supplemented with 0.03% Tween 20) and fasted (0.1 N HCl) states. In vitro results suggest that the presence of ethanol will not cause dose dumping when Oxycodone DETERx is taken with food. (3.2.P.2.2 Drug Product, page 174)
13.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	x	☐	
14.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	x	☐	
	REGIONAL INFORMATION AND APPENDICES				
15.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	x	☐	
16.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	☐	☐	
17.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	x	
18.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is			x	

C. FILING CONSIDERATIONS					
	equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

Risk Assessment

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	1	2	Release (1) Stability (3)	Release (2) Stability (6) (low)	The drug product has a 2 year proposed shelf life at 25 °C. Impurity (b) (4) The specification for unidentified impurities is NMT (b) (4) %.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	4	24 (low)	(b) (4)
Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	3	4	36 (medium)	(b) (4)
Microbial Limits	• Formulation • Raw materials • Process	1	2	3	6 (low)	(b) (4)

	parameters • Scale/equipment • Site					
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping	4	4	4	64 (high)	Alcohol dose dumping - opioid

CMC Assessmet

Xtampza ER is an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone. The formulation provides analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. The capsule formulation contains microspheres with a median particle size of approximately (b) (4) microns. The microspheres contain oxycodone base, (b) (4)

The capsules are manufactured in 5 capsule strengths containing the equivalent of 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxycodone hydrochloride (HCl). The corresponding capsules sizes are size 3, 2, 1, 0, and 00. During formulation and clinical development, Oxycodone capsule strengths were expressed as oxycodone HCl-equivalent strengths. Based on the United States Pharmcopeia (USP) Salt Policy and Food and Drug Administration (FDA) feedback (Pre-NDA Meeting Minutes, Module 1.6.3), the commercial strengths will be expressed in terms of oxycodone base (9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg). Oxycodone DETERx capsules are packaged in 100-count, round, white, high-density polyethylene bottles of different sizes depending on the capsule strength; bottle sizes of 60 cc, 100 cc, 120 cc, 150 cc and 200 cc are used for the 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg oxycodone HCl-equivalent strengths, respectively. The bottles are (b) (4) capped with (b) (4) child-resistant caps. (b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Review Issues Identified:

No review issues have been identified at this time.

CMC comments for 74-Day Letter:

1. Per ICH Q6A, provide an additional test for the identification of the API in the drug product.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf

BIOPHARMACEUTICS ASSESSMENT

SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

Collegium Pharmaceutical, Inc. is submitting Oxycodone DETERx®, an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone (base). The hydrochloride salt of this agent has been used medically since 1917 and thus has an extensive clinical history. The formulation provides analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Currently, there is an extended release (ER) tablet of oxycodone in the market (OxyContin® [oxycodone hydrochloride extended-release tablets] (approved by the FDA on 2014, Stamford, CT, Purdue Pharma L.P.), which contains a relatively large dose of drug and is attractive to abusers as the time-release mechanism can be defeated by relatively simple manipulations including chewing or crushing the tablet. Oxycodone DETERx® has been developed to address these and other limitations of currently marketed ER opioid products.

Drug Product:

Oxycodone DETERx®, is an abuse-deterrent, extended-release, microsphere-in-capsule, oral formulation of the active ingredient oxycodone (base). The microspheres are formed (b) (4) [redacted] and encapsulated to produce capsules that contain oxycodone in an amount equivalent to 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg oxycodone HCl.

According to the Applicant, sprinkling capsule contents on several soft foods prior to in vitro dissolution does not impact the in vitro dissolution profile relative to intact capsules. Passing capsule contents through enteral tubes of various dimensions (simulating NG or G tubes) with the aid of various liquid vehicles does not impact the in vitro dissolution profile relative to intact capsules. Also, the Applicant stated that opening the capsules and crushing or chewing prior to fed state administration did not significantly affect PK (to be qualified by the OCP review team).

Dissolution results for DETERx 40 mg Capsules after Particle Size Reduction (PSR) compared with control utilizing several techniques indicated that the largest difference in in vitro release was seen for the mortar and pestle, which yielded a dissolution difference of <20% at all time points over 12 hours compared with intact control. Dissolution studies (40 mg Capsule Strength) in Fed Media with 0%, 4%,10%, 20% and 40% Ethanol through 24 Hours were performed, DETERx at 40%, 20%, and 4% ethanol were found to be equivalent to or slower than for 0% ethanol, suggesting that the presence of alcohol will not cause dose dumping when Oxycodone DETERx is taken with food. According to the Applicant, in vivo study confirmed these results.

Review:

The biopharmaceutics review will be focused on the evaluation and acceptability of the data provided to support; 1) Dissolution method and acceptance criterion, 2) (b) (4) ; 3) The dissolution similarity between crushed drug product and intact drug product; and4) Alcohol dose dumping study.

Review Issues Identified:

None from biopharmaceutics perspective

Biopharmaceutics Comments for 74-Day Letter:

Provide the following information/data:

1. We acknowledge the data submitted to determine the impact of several particle size reduction (PSR) techniques on the release of your proposed product. It is also noted that the proposed QC method was used to assess the percent release over time. Provide data justifying the suitability of the dissolution method used for assessing the dissolution rate of the "pulverized" drug product. Specifically, provide data demonstrating that the in vitro release results submitted are not confined by the use of an inappropriate dissolution technique.
2. There is no IVIVC approved for your proposed product. Therefore, the selection of the dissolution acceptance criteria limits should be based on the mean target (biobatches) value ± (b) (4)% and NLT (b) (4)% for the last specification time-point. Implement these acceptance criteria for your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test. Also, provide justification for the selected last specification time point (i.e. (b) (4) hrs) when more than (b) (4)% of the drug is released within 12 hours.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Fang Wu -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Fang Wu -A, 0.9.2342.19200300.100.1.1=2000994797
Date: 2015.02.09 06:15:17 -05'00'

Fang Wu, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Products

Sandra Suarez -A

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Date: 2015.02.09 08:32:17 -05'00'

Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Quality Assessment Lead
Office of New Drug Products

Ciby J. Abraham -A

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -A
Date: 2015.02.09 14:39:00 -05'00'

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

Julia C. Pinto -A

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Date: 2015.02.10 16:56:11 -05'00'

Julia C. Pinto, Ph.D.
Acting Branch Chief
OPQ/ONDP/DIVII/Branch IV

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 208090 **Applicant:** Collegium Pharmaceutical, Inc. **Letter Date:** 12 December 2014

Drug Name: Oxycodone DETERx® **NDA Type:** 505(b)(2) **Stamp Date:** 12 December 2014

Dosage Form: Capsule **Reviewer:** Erika Pfeiler, Ph.D.

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
4	Has the applicant submitted the results of analytical method verification studies?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable)?			N/A
6	Is this NDA fileable? If not, then describe why.	X		

Erika Pfeiler, Ph.D. Date
Microbiologist

Stephen Langille, Ph.D. Date
Senior Review Microbiologist

The following comment should be conveyed to the applicant in the 74-day letter.
Your application states that microbial limits testing will be performed for release and stability using methods described in USP <61> and USP <62>. State whether method verification studies were performed to ensure that these methods are adequate for use with your drug product.

Erika A. Pfeiler -S

Digitally signed by Erika A. Pfeiler -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396533, cn=Erika A. Pfeiler -S
Date: 2015.01.15 09:20:56 -05'00'

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

/s/

ROBYN S JORDON
05/04/2016