

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204031Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: Feb 7, 2014

FROM: Yong Hu, Ph.D.

SUBJECT: Addendum to Chemistry Review #1 for NDA 204031 (Oxycodone hydrochloride (OC) and acetaminophen (APAP) extended-release tablets)

TO: NDA 204031 file

This addendum is primarily to evaluate the methods of the in-vitro extraction studies used to characterize the abuse liability of the product from a chemistry perspective. The addendum will not assess the abuse-deterrence claims in the labeling.

(b) (4)



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/s/

YONG HU
02/14/2014

PRASAD PERI
02/14/2014
I concur

NDA 204031

**Oxycodone Hydrochloride/Acetaminophen
Extended-Release Tablet**

Mallinckrodt Inc.

Yong Hu, Ph.D.

**Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment**

For

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

1. NDA: 204031
2. REVIEW #: 1
3. REVIEW DATE: 10/28/2013
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA
Response to filing comments
Quality response to information request

5/24/2013
8/12/2013
10/4/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Mallinckrodt Inc.
Address: 675 McDonnell Blvd.,
Hazelwood, MO 63042
Representative: Kevin Healy,
Associate Director Regulatory Affairs
Telephone: 919-469-3574 Ext 53513

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Xartemis XR

Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Oxycodone Hydrochloride/Acetaminophen Extended-Release Tablet
- c) Code Name/# (ONDC only): COV795; MNK795.
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

505 B(2); Listed Drug: Roxicodone (15 mg OC tablet, NDA 21011; Mallinckrodt) ; Ultracet (325 mg APAP/37.5 mg tramadol HCl tablet, NDA 21123; Janssen Pharms)

10. PHARMACOL. CATEGORY:

Acetaminophen does not have an established pharmacological class and its mechanism of action is not clear. Oxycodone is an opioid agonist.

11. DOSAGE FORM:

Extended-release tablet

12. STRENGTH/POTENCY:

7.5 mg oxycodone HCl / 325 mg acetaminophen

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

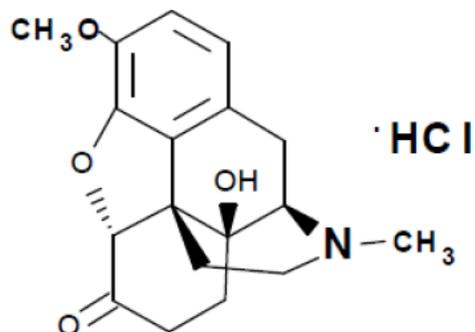
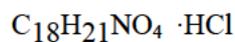
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Oxycodone Hydrochloride:

Chemical Names

Chemistry Review Data Sheet

- a) Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5 α)-.
b) 4,5 α -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

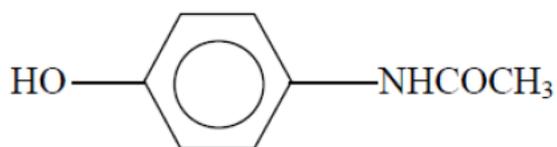
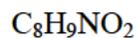
**Molecular Formula****Molecular Weight**

351.83

Acetaminophen:

Chemical Names

1. N-acetyl-p-aminophenol
2. 4'-hydroxyacetanilide

**Molecular Formula****Molecular Weight**

151.16

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
5326	II	Mallinckrodt	Acetaminophen	1	Adequate	9/16/2013	
6930	II	Mallinckrodt	Oxycodone HCl	1	Adequate	7/9/2013; 8/29/2012	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104702	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Acceptable	10/24/2013	
Pharm/Tox	The drug substance and drug product impurities specifications are qualified. The drug product excipients are acceptable.		Dr. Beth Bolan
Biopharm	The dissolution specification is acceptable. The proposed IVIVR is not acceptable.		Dr. Sandra Suarez
LNC	The dosage form should be called “extend-release tablet” instead of (b) (4) , initially proposed by the applicant.		
Methods Validation	The product is not an NME. The methods		

Chemistry Review Data Sheet

	are conventional in nature. No method validation was requested.		
OPDRA	Not applicable.		
EA	Not requested. Categorical exclusion.		
Microbiology	The NDA for Xartemis does not include a Microbial Limits release specification for drug product release or stability; however, the applicant provides a suitable rationale for the exclusion of this testing. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.	6/10/2013	Dr. John Metcalfe

The Chemistry Review for NDA 204031

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for Approval pending the applicant's satisfactory response to the labeling issues.

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

None.

II. Summary of Chemistry Assessments

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

The drug product is a bilayer extended-release tablet, comprised of an immediate release (IR) layer and an extended release (ER) layer. The tablet contains 7.5 mg oxycodone hydrochloride and 325 mg acetaminophen. The IR layer contains (b) (4) % of the total oxycodone HCl and (b) (4) % of the total acetaminophen dose, whereas the ER layer contains (b) (4) % of the total oxycodone HCl and (b) (4) % of the total acetaminophen dose.

The applicant claims that the product has been developed using the Depomed AcuForm® GR drug delivery technology, which utilizes gastro-retention to target release of drug to the upper gastrointestinal (GI) tract over an extended period of time. The tablets were observed to swell when exposed to water and simulated gastric fluids overtime.

The product is a modified oval-shaped blue tablet with a debossed logo of an "M" in a box over "115" on the IR side of the tablet.

The following two container closure systems will be used for the commercial product.

HDPE bottles: 100-count, 150 cc high-density polyethylene (HDPE) bottles with a (b) (4) closure; Each bottle contains two, 1 g silica gel desiccant canisters, for a total of 2 g of desiccant and is induction sealed with an aluminum inner seal.

Blister Packs: 10 tablets per blister card; 10 cards per carton. The blister is composed of (b) (4) sealed with aluminum. (b) (4)

Executive Summary Section

The product is intended to have abuse-deterrent characteristics compared to the reference product, Percocet, which is an IR tablet of the same strengths as the proposed product. However, the Controlled Substance Staff has not agreed to any abuse-deterrence claims that can be made in the labeling.

The proposed commercial product is the same as the phase III clinical trial product except that the commercial tablets have a debossed logo described above. The Biopharmaceutics reviewer concludes that the debossing does not affect the tablet dissolution. The (b) (4) polymer in the ER layer is polyethylene oxide (Polyox (b) (4)), for which a suitable viscosity range has been established to support the tablet dissolution targets. At the pre-NDA meeting the FDA agreed that results of dissolution testing do not indicate potential for dose dumping in the presence of alcohol, and that an in vivo study will not be necessary.

The product is manufactured at (b) (4), which has been deemed acceptable in the Establishment Evaluation System (EES). The manufacturing process involves (b) (4)

The manufacturing process and site for the commercial product are the same as those for the phase III and primary stability batches.

The drug substance information is provided in the DMF 5326 (acetaminophen) and DMF 6930 (oxycodone HCl), both of which have been deemed adequate to support ANDAs. The oxycodone HCl and acetaminophen drug substances are manufactured by Mallinckrodt, Inc. in St. Louis, Missouri and in Raleigh, North Carolina, respectively. Both manufacturers have been deemed acceptable in the Establishment Evaluation System (EES). The oxycodone HCl drug substance, Code 8873, has a low level (up to (b) (4)%) of the impurity 14-hydroxycodone (USP related compound A), an (b) (4). In the comparability protocol, the applicant proposes a (b) (4)

According to an FDA General Advice Letter issued to the DMF holder, the (b) (4)% specification limit is acceptable for a maximum daily dose of (b) (4) of oxycodone HCl (b) (4).

The drug product stability data cover 12-month storage under the long-term (25°C/60% RH) and intermediate (30°C/65%RH) conditions and 6-month storage under the accelerated (40°C/75%RH) condition. A trend of change was observed for the oxycodone degradation product (b) (4), the total oxycodone degradation products, and the tablet dissolution. However, the (b) (4) level is the stability-limiting factor.

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

The product is indicated for the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate. The recommended dose is 2 tablets every 12 hours without

Executive Summary Section

regard to food. The tablet should be swallowed whole without crushing, splitting, or chewing and with plenty of water.

The product is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

The expiration dating periods of 24 months for the product in 100-count, 150 cc HDPE bottles and 18 months in 10-count unit dose blisters are acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The NDA contains adequate information to assure the identity, purity, strengths and performance of the drug product. The Office of Compliance has deemed all the manufacturing and testing facilities for the drug substances and drug product “Acceptable”. There are deficiencies in the labeling from CMC perspective. Once the deficiencies are addressed, the NDA can be approved.

III. Administrative**A. Reviewer’s Signature**

See DARRTS.

B. Endorsement Block

See DARRTS.

C. CC Block

See DARRTS.

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/s/

YONG HU
10/28/2013

PRASAD PERI
10/28/2013
I concur

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204-031
Submission Date	5/28/2013
Product name, generic name of the active	Xartemis (oxycodone hydrochloride and acetaminophen)
Dosage form and strength	Tablets; 7.5 mg oxycodone hydrochloride / 325 mg acetaminophen
Applicant	Mallinckrodt Inc.
Clinical Division	DAAAP
Indication	the management of (b) (4) acute pain
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

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

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		See the Initial Assessment section for the proposed dissolution method and acceptance criteria.
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	Not applicable.
6.	Is there information provided to support the biowaiver request?		x	Not applicable.
7.	Does the application include a IVIVC model?	x		The Applicant developed a physiologically based pharmacokinetic (PK) model to establish an in vitro in vivo relationship for oxycodone hydrochloride and acetaminophen from COV795.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant reports that oxycodone hydrochloride is considered a BCS Class (b) (4) compound and that acetaminophen is considered a BCS Class (b) (4) compound.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

9.	Is information on mixing the product with foods or liquids included?		x	Not applicable.
10.	Is there information on the effect of alcohol on in vitro drug release	x		
11.	Is there any in vivo BA or BE information in the submission?	x		These data will be reviewed by the Clinical Pharmacology Reviewer.

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
12.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	
14.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See the Initial Assessment section.

{See appended electronic signature page}

Karen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

6/28/2013
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

6/28/2013
Date

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

INITIAL ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

This submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criteria for oxycodone hydrochloride (OC) and acetaminophen (APAP), and an *in vitro in vivo relationship* (IVIVR).

The clinical development program for the proposed product consisted of 11 Phase 1 PK studies, one Phase 1 human abuse liability study, and two Phase 3 studies. The Phase 3 program consisted of 1 randomized, double-blind, placebo-controlled efficacy study and 1 open-label safety study. The to-be-marketed formulation was used in 5 clinical PK studies, including single- and multiple-dose studies comparing it to the listed drugs, Roxicodone (15 mg OC) and Ultracet (37.5 mg tramadol/325 mg APAP). Additionally, the to-be-marketed formulation was used in the two Phase 3 studies.

The proposed dissolution method:

USP Apparatus	Rotation Speed	Media Volume	Temperature	Medium
2	100 rpm	900 mL	37 °C	0.1N HCl

The proposed acceptance criteria:

Acceptance Criteria for Oxycodone HCl	
(b) (4)	at 0.50 hour
(b) (4)	at 2 hour
(b) (4)	at 4 hour
NLT (b) (4)	at (b) (4)

Acceptance Criteria for Acetaminophen	
(b) (4)	at 0.50 hour
(b) (4)	at 2 hour
(b) (4)	at 4 hour
NLT (b) (4)	at (b) (4)

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the proposed dissolution acceptance criteria for oxycodone hydrochloride and acetaminophen, 3) results from the *in vitro* alcohol dose dumping studies and 3) the IVIVR.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 204031 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

To aid the review of the NDA submission, the following comments will be conveyed to the Applicant:

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

1. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the proposed dissolution acceptance criteria (i.e., specification-sampling time points and values) for your proposed product.

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/s/

KAREEN RIVIERE
06/28/2013

ANGELICA DORANTES
06/28/2013

**Initial Quality Assessment
Office of New Drug Quality Assessment
Division of Pre-Marketing Division III, Branch I**

OND Division: Anesthesia, Analgesia and Addiction
NDA: 204031
Applicant: Mallinckrodt, Inc
Stamp date: May 28, 2013
PDUFA Date: November 28, 2014
Trademark: NA
Established Name: Oxycodone HCl and Acetaminophen (COV795 and MNK795)
Proposed Name: Xartemis
Dosage Form: Controlled Release Tablets (7.5mg/325mg)
Route of Administration: Oral
Indication: Management of (b) (4) acute pain

Pharmaceutical Assessment Lead: Julia C. Pinto, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	<u>√</u>	_____

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), priority NDA with 6-month review clock. It is a combination product consisting of oxycodone HCl (OC) and acetaminophen (APAP), co-formulated within a multilayer, abuse-deterrent tablet comprising an IR layer and a extended release (ER) layer. No critical issues are identified in this initial assessment. All manufacturing facilities are entered into EES and submitted to Compliance for inspection. Consults to the Microbiology and Biopharmaceutics Teams have been sent. This NDA is therefore considered fillable from the CMC perspective, with one comment for the 74-Day letter.

Comment for 74-Day Letter:

1. Release testing of the drug product should include testing for tablet hardness according to USP 1217.
2. Demonstrate whether the intact tablet will swell in water and in simulated gastric fluids over time. Provide tablet dimensions and photos of the tablet at various time points.

B. Review: Drug Substance I: Acetaminophen (APAP)

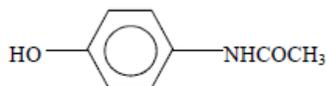
Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

The first of two APIs is Acetaminophen.

Acetaminophen, Paracetamol APAP

Chemical Names

1. N-acetyl-p-aminophenol
2. 4'-hydroxyacetanilide
3. p-hydroxyacetanilide
4. p-acetamidophenol
5. p-acetaminophenol
6. p-acetylaminophenol



Molecular Formula

C₈H₉NO₂

Molecular Weight

151.16

Characterization, Manufacture, Control, and Impurities

Acetaminophen is manufactured by Mallinckrodt in the Raleigh Pharmaceutical Plant, NC. Characterization, description of the manufacturing processes and controls are referenced to the Drug Master File (DMF) 5326, last reviewed as adequate April 08, 2013 by M. Pineiro-Sanchez

(b) (4)

(b) (4)

Drug Substance Specifications for APAP

Specifications for APAP are shown below. It is controlled according to the current USP monograph for APAP.

Table 2.3.S.4.1-1 Tests and Specifications for APAP

Test	Acceptance Criteria
APPEARANCE AND ODOR	White crystalline powder. Odorless.
IDENTIFICATION A (Infrared Absorption)	To Match standard
IDENTIFICATION B (Ultraviolet Absorption) ¹	To Match standard
IDENTIFICATION C (TLC) ¹	To Match standard



(b) (4)

¹ Results may be accepted from the Mallinckrodt's (Raleigh, North Carolina Facility) Certificate of analysis in lieu of testing by (b) (4)

Analytical Methods and Validations for APAP:

The methods for the evaluation of APAP API are compendial except for the related substance HPLC method which was developed in-house by Mallinckrodt. A validation report for the HPLC method is provided in the submission.

Table 2.3.S.4.2-1 Test Methods

Test	Method
PHYSICAL EXAMINATION	VISUAL
(b) (4)	

Batch analysis:

The certificates of analysis from the drug substance supplier, Mallinckrodt Inc., and (b) (4) the drug product manufacturer, for the lots of acetaminophen used to make the drug product batches are submitted in the application.

Reference standard:

RS001 is the reference standard utilized for Acetaminophen USP and a COA is provided.

Container Closure System:

Referenced to DMF (b) (4)

Drug substance Stability:

Referenced to DMF 5326

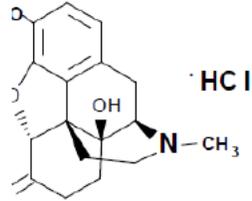
B. Review: Drug Substance II : Oxycodone HCl

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

The second API in the drug product composition is oxycodone HCl. Structure and chemical names are shown below.

Generic Name

- a) Oxycodone Hydrochloride
- b) 14-Hydroxy-7,8-dihydrocodeinone Hydrochloride



Chemical Names

- a) Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-.
- b) 4,5 α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Characterization, Manufacture, Control, and Impurities

Oxycodone HCl is manufactured by Mallinckrodt in the St. Louis, Missouri under DMF 6930. Characterization, description of the manufacturing processes and controls are referenced to the Drug Master File (DMF) 6930, last reviewed as adequate November 1, 2012 by S. Bain (Review 18) . (b) (4)

(b) (4) . Process impurities include those listed in the following table:

Table 2.3.S.3.2-1 Oxycodone HCl USP (Mallinckrodt Code 8873)

Impurity Name	Impurity Structure	PhEur	Origin	Specification
Oxymorphone				(b) (4)
				(b) (4)

Impurity Name	Impurity Structure	PhEur	Origin	Specification
6-Oxycodol				(b) (4)
				(b) (4)
14-Hydroxycodone				(b) (4)

Impurity Name	Impurity Structure	PhEur	Origin	Specification
Codemone				(b) (4)
Noroxycodone				(b) (4)

Drug Substance Specifications for Oxycodone HCl

Specifications for Oxycodone HCL are shown below. The release and testing is accordance with the USP monograph for Oxycodone HCl.

Table 2.3.S.4.1-1 Tests and Specifications for Oxycodone Hydrochloride USP

Test	Specification
PHYSICAL EXAMINATION	White to off-white fine crystalline powder
IDENTIFICATION A (Melting Range)(USP<741>)	218° - 223°C
MELTING RANGE	2 degrees Celsius range
IDENTIFICATION B (IR)(USP<197K>)	Matches Reference Standard
SPECIFIC ROTATION (USP<781S>)	-137° to -149°
RESIDUE ON IGNITION(USP<281>)	0.05% max
(b) (4)	
ASSAY (anhydrous basis) ¹	
OXYCODONE HCl	97.0 - 103.0% w/w
RELATED COMPOUNDS ¹	
(b) (4)	



Analytical Methods and Validations for APAP:

The methods for the evaluation of APAP API are compendial except for the related substance HPLC method which was developed in-house by Mallinckrodt. A validation report for the non-compendial method is provided in the submission.

Batch analysis:

The certificates of analysis from the drug substance supplier, Mallinckrodt Inc., (b) (4) the drug product manufacturer, for the lots of oxycodone used to make the drug product batches are submitted in the application.

Reference standard:

RS023, lot number 1582 H12583 the reference standard utilized for Oxycodone Base. A COA is provided.

Container Closure System:

Referenced to DMF (b) (4)

Drug substance Stability:

Referenced to DMF (b) (4)

Drug product

COV-795 tablets are multilayer extended release, oval-shaped, blue-coated tablets that use the Depomed AcuForm® GR drug delivery technology. This technology utilizes gastroretention to target release the drug to the upper gastrointestinal (GI) tract over an extended period of time. COV795 was formulated to comprise an immediate release (IR) layer and a gastroretentive extended release (ER) layer. The IR layer contains (b) (4)% of the total OC and (b) (4)% of the total APAP dose, whereas the ER layer contains (b) (4)% of the total OC and (b) (4)% of the total APAP dose. The product is formulated as an abuse-deterrent composition. The results from extraction studies (b) (4) as well as a dose-dumping study is provided. The commercial tablet will have a debossed logo of an "M" in a box over "115" on one side of the tablet. The tablet is formulated in one strength of 7.5mg OC/325mg APAP. The composition of each layer and coating is shown in the table below. Excipients are all compendial and no novel excipients are used.

Table 3.2.P.1-1: Components and Composition of COV795 by Layer (7.5 mg OC/325 mg APAP)

(b) (4)							
Ingredient	Grade	Role	mg in Tablet	w/w %			
Oxycodone HCl ¹	USP	Active	1.875	0.197%			
Acetaminophen	USP	Active	162.500	17.073%			
Hydroxypropyl Cellulose	(b) (4) NF	(b) (4)	(b) (4)	(b) (4)			
Microcrystalline Cellulose	(b) (4) NF						
Croscarmellose Sodium	(b) (4) NF						
Colloidal Silicon Dioxide	(b) (4) NF						
Magnesium Stearate	NF						
Pregelatinized Starch	(b) (4) NF						
Citric Acid Anhydrous Powder	USP						
Edetate Disodium	USP						
Polyethylene Oxide (Polyox molecular weight =	(b) (4) (b) (4)				NF	Controlled Release Polymer	(b) (4) (b) (4)

Drug Product Manufacture:

The product is manufactured in a multistep process according to the Flow Chart below. Detailed discussions of the process, the critical steps and controls are provided in sections 3.2.P.3.3 and P.3.4.



Drug Product Specifications:

Specifications for the multilayer tablet are shown below. These include controls for degradants in both APIs. Moisture content is monitored, but tablet hardness is not included in the release testing. Since the tablet is coated, friability testing may not be necessary. A comment regarding the inclusion of tablet hardness testing is sent in the 74-day letter.

Table 3.2.P.5.1-1: Proposed Drug Product Release and Stability Specifications for COV795

Tests	Release Specifications	Stability Specifications	^{(b) (4)} Analytical Standard (Comprises Specifications and Test Methods) ¹
^{(b) (4)}			

Table 3.2.P.5.1-1: (Continued)

Tests	Release Specifications	Stability Specifications	(b) (4) Analytical Standard (Comprises Specifications and Test Methods) ¹
(b) (4)			

Batch Analysis

Batch analysis data on the batches of drug product used in the clinical studies, according to the following table is provided in the submission. COA’s are also included.

Table 3.2.P.5.4-1: Summary of Phase I Clinical Supply, Phase III Clinical Supply, and Registration Batches for COV795 (7.5 mg OC/325 mg APAP)

Drug Product Batch Number / COA Link	Lot Usage	Date of Manufacture	Lot Size ²	Oxycodone HCl (b) (4) Drug Product Manufacturing Site) Lot Number	Oxycodone HCl Mallinckrodt Lot Number ¹	Acetaminophen (b) (4) Drug Product Manufacturing Site) Lot Number	Acetaminophen Mallinckrodt Lot Number
A78056	Phase I Pharmacokinetic Study; Phase III Open Label Clinical Study	(b) (4)		A67495	1006000252	A62522	004810A128
A79956	Phase III Blinded Clinical Study; Human Abuse Liability Study	(b) (4)		A67495	1006000252	A62522	004810A128
A82672	Registration	(b) (4)		A67496A (ER) ¹ A70412A (IR) ¹	1006000175 (ER) (IR) 1010000386 (IR)	A71266A	004810K358
A82673	Registration	(b) (4)		A70412A (ER) ¹ A70413A (IR) ¹	1010000386 (ER) (IR) 1010000319 (IR)	A71267A	004810K357
A82674	Registration	(b) (4)		A70413A (ER) ¹ A67496A (IR) ¹	1010000319 (ER) (IR) 1006000175 (IR)	A71268A	004810K433

¹ Differing lots of oxycodone HCl were used in the manufacture of the immediate release (IR) and extended release (ER) (b) (4)

² Theoretical number of coated tablets

Container Closure:

Two container closure systems and packaging configurations will be used for the commercial product. These are: HDPE bottles: 100 count, 150 cc bottles with a 38 mm closure; Blister Packs: 10 tablets per blister card; 10 cards per carton. Each 100 count bottle contains two, 1 g desiccant canisters, for a total of 2 g of desiccant per Bottle

Stability:

Stability data on three registration batches and several clinical batches is provided in this submission. The Data includes 12 months under long term, 12 months intermediate and 6 months under accelerated conditions to support a proposed expiry of 24 months for the drug product in HDPE bottles and 18 months for the DP stored in blister packages. Data from a photostability study is also provided.

D. Comments for 74-day Letter:

1. Release testing of the drug product should include testing for Tablet Hardness and Friability.
2. Demonstrate whether the intact tablet will swell in water and in simulated gastric fluids over time. Provide tablet dimensions and photos of the tablet at various time points.

E. Recommendation for fileability: The NDA is considered fileable based on data provided in the May 28, 2013 submission, for the drug product packaged in HDPE bottles and blister packages with 12-month long term/6-month accelerated stability data. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for a team review.

Consults:

1. Microbiology Team
2. Biopharmaceutics, ONDQA

NDA Number: 204031

Supplement Number and Type:

Established/Proper Name:

Oxycodone HCl/Acetaminophen

Applicant: Mallinkrodt

Letter Date: 05/24/2013

Stamp Date: 05/28/2013

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 104702

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for (b) (4) API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		<p>Malinckrodt, DMF 5326 (APAP) Malinckrodt, DMF 6930 (OC)</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF 5326 (APAP) and DMF 6930 (OC)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF 5326 (APAP) and DMF 6930 (OC)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF 5326 (APAP) and DMF 6930 (OC)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?	X		Referenced to DMF 5326 (APAP) and DMF 6930 (OC)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

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

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		Based on pre-NDA agreements and sufficient data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

Julia C. Pinto, Ph.D.
CMC Lead, ONDQA

6/20/2013
Date

Prasad Peri, Ph.D.
Branch II Chief, ONDQA

6/20/2013
Date

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

/s/

JULIA C PINTO
06/24/2013

PRASAD PERI
06/24/2013
I concur