

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204031Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204031

SUPPL # n/a

HFD # 170

Trade Name: Xartemis XR

Generic Name: oxycodone hydrochloride/acetaminophen extended-release tablets

Applicant Name: Mallinckrodt, Inc.

Approval Date, If Known: March 3, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

n/a (product has two APIs) YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 007337	Percodan (oxycodone hydrochloride/aspirin) tablets
NDA# 200534	Oxycodone hydrochloride capsule
NDA# 200535	Oxycodone hydrochloride oral solution
NDA# 201194	Oxycodone hydrochloride oral solution
NDA# 022272	OxyContin (oxycodone hydrochloride) extended-release tablet
NDA# 202080	Oxecta (oxycodone hydrochloride) tablet
NDA# 021011	Roxicodone (oxycodone hydrochloride) tablet
NDA# 022450	Ofirmev (acetaminophen) intravenous solution
NDA# 021123	Ultracet (tramadol hydrochloride/acetaminophen) tablet
NDA# 020232	Fioricet with Codeine (acetaminophen/ butalbital/ caffeine/ codeine phosphate) tablet

And numerous ANDAs for products containing oxycodone hydrochloride and/or acetaminophen (refer to the Orange Book for complete listings).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should

only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

n/a

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently

support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

n/a

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

n/a

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study COV15000182: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Evaluation of the Safety and Analgesic Efficacy of COV795 (Oxycodone HCl/Acetaminophen) ER Tablets in Moderate to Severe Postoperative Bunionectomy Pain Followed by an Open-Label Extension

Study COV15000181: An Open-Label Safety Study of COV795 in Subjects with Osteoarthritis or Chronic Low Back Pain

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

n/a

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

n/a

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study COV15000182: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Evaluation of the Safety and Analgesic Efficacy of COV795 (Oxycodone HCl/Acetaminophen) ER Tablets in Moderate to Severe Postoperative Bunionectomy Pain Followed by an Open-Label Extension

Study COV15000181: An Open-Label Safety Study of COV795 in Subjects with Osteoarthritis or Chronic Low Back Pain

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by"

the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 104702 YES ! NO
! Explain:

Investigation #2 !
!
IND # 104702 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

n/a

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

n/a

Name of person completing form: Dominic Chiapperino, PhD
Title: Senior Regulatory Health Project Manager
Date: February 24, 2014

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

DOMINIC CHIAPPERINO
03/03/2014

SHARON H HERTZ
03/03/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204031	NDA Supplement #: Not applicable (n/a)	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Xartemis XR Established/Proper Name: oxycodone hydrochloride and acetaminophen Dosage Form: Extended-release tablets		Applicant: Mallinckrodt, Inc. Agent for Applicant (if applicable): n/a
RPM: Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager		Division: Division of Anesthesia, Analgesia, and Addiction Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>February 28, 2014</u>. Actual approval, March 11, 2014 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 3, new formulation
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): AP, on 3/11/14
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included (2/24/14)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included (5/28/13)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included (2/24/14)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included (5/28/13)
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included (11/22/13)
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	Letter determining “acceptable” 10/3/13, Holquist Review, 10/1/13, Border-Hemphill and Wilkins Parker
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: (See SRPI review that is part of filing review, 8/23/13, Chiapperino) DMEPA: 2/3/14, Borders-Hemphill and Chan; 10/11/13, Borders-Hemphill and Wilkins Parker DMPP/PLT: 11/7/13, Mills, Fox, Fuller, and Griffiths OPDP: 11/7/13, Fox SEALD: 2/24/14, Adebowale and Brodsky CSS: See completed CSS reviews for labeling recommendations Other: PMHS/Maternal Health team: 10/30/13, Sahin, Best, and Yao Other: PMHS/Pediatric Team: 10/24/13, Radden, Sachs, and Yao

Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee 	505(b)(2) Assessment, 3/3/14, Chiapperino (Cleared by committee on 11/13/13) RPM filing review, 8/23/13, Chiapperino
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included (3/3/14)
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (approvals only) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/2/13</u> If PeRC review not necessary, explain: _____ 	PeRC Minutes, 11/6/13, Greeley
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (do not include previous action letters, as these are located elsewhere in package)	Reverse-chronologically ordered letters and emails (includes NDA acknowledgement, Filing, Clock Extension, and many information requests, etc)
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (indicate date of mtg) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (indicate date of mtg) 	Meeting minutes, 1/7/13 (meeting held on 12/13/12)
<ul style="list-style-type: none"> • EOP2 meeting (indicate date of mtg) 	Pre-Phase 3 Meeting Preliminary Comments, 12/7/11 (meeting cancelled)
<ul style="list-style-type: none"> • Mid-cycle Communication (indicate date of mtg) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (indicate date of mtg) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs) 	n/a

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	Summary review, 3/11/14, Hertz
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	CDTL memo #2, 2/24/14, Fields; CDTL memo #1, 11/7/13, Fields
PMR/PMC Development Templates (<i>indicate total number</i>)	Total of 3 templates, 2/27/14, Chiapperino and Racoosin
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Memo addressing clock extension, 11/20/13, Fields and Rappaport
• Clinical review(s) (<i>indicate date for each review</i>)	Review, 10/27/13, Kilgore and Fields; filing review, 7/3/13, Kilgore and Fields
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See page 16 of clinical review, 10/27/13, Kilgore and Fields
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	Review #2, 2/14/14, Tolliver, Calderon, and Klein; Review #1, 11/4/13, Tolliver, Calderon, and Klein
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	Review #2, 1/28/14, Wilkins Parker and Manzo (Concludes REMS not necessary); review #1, 10/17/13, Smith and Lehrfeld; Most recent version of submitted REMS prior to conclusion that REMS not needed:
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Letter, 11/19/13, Lee and Pohlman; letter, 11/19/13, Lee and Pohlman; audit summary, 10/17/13, Lee, Pohlman, and Ayalew; letter, 10/17/13, Lee and Pohlman

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	Review, 10/25/13, Li and Derr; consult stats review#2 for CSS, 10/9/13, Sun and Tsong; stats consult review #1 for CSS, 8/26/13, Lancaster and Tsong; filing review, 7/3/13, Li and Derr
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	Review, 10/28/13, Qiu and Xu; filing review, 6/28/13, Qiu and Xu
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Review, 10/25/13, Bolan and Mellon; filing review, 6/27/13, Bolan and Mellon
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	CMC review #2, 2/14/14, Hu and Peri; CMC review #1, 10/28/13, Hu and Peri; biopharm review, 10/25/13, Suarez and Dorantes; biopharm filing review, 6/28/13, Riviere and Dorantes; CMC filing review, 6/24/13, Pinto and Peri
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	Combined filing and primary review, 6/11/13, Metcalfe and Langille
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 112 of CMC review #1, 10/28/13, Hu and Peri
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 10/23/13 (see page 114-115 of CMC review #1, 10/28/13, Hu and Peri) <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per CMC review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

DOMINIC CHIAPPERINO
03/12/2014



NDA 204031

MEETING DENIED

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Kevin D. Healy
Associate Director Regulatory Affairs

Dear Mr. Healy:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablets, 7.5 mg/325 mg.

We also refer to your correspondence dated December 20, 2013, requesting a type A meeting to discuss abuse deterrent (AD) features claimed for Xartemis XR. We are denying the meeting because we do not agree with your characterization of your program to obtain oral AD claims as being stalled or with your statement that FDA has not provided definitive advice related to this program.

(b) (4)

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DOMINIC CHIAPPERINO
01/02/2014



NDA 204031

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Kevin D. Healy
Associate Director Regulatory Affairs

Dear Mr. Healy:

Please refer to your New Drug Application (NDA) dated May 24, 2013, received May 28, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablet, 7.5 mg/325 mg.

On November 19, 2013, we received your November 18, 2013, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 28, 2014.

In addition, although we had already begun communicating labeling changes and postmarketing requirements/commitments to Mallinckrodt, we are establishing a new timeline for communicating further necessary labeling changes or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any additional postmarketing requirement/commitment requests by January 31, 2014.

If you have any questions, call Dominic Chiapperino, PhD, Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PARINDA JANI
11/21/2013



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND ADDICTION PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

Memorandum

DATE: November 20, 2013

FROM: Ellen Fields, MD, MPH
Clinical Team Leader
DAAAP

THROUGH: Bob Rappaport, MD
Division Director
DAAAP

SUBJECT NDA 204031/ SN 0014
Xartemis XR (oxycodone/acetaminophen extended-release tablets)
Quality Information Amendment Abuse Assessments
Review clock extension

NDA 204031 for Xartemis XR (oxycodone 7.5 mg/ acetaminophen 325 mg extended-release tablets) is currently under review for the treatment of acute pain. The PDUFA goal date for this application is November 28, 2013. The Xartemis XR formulation is intended to possess abuse deterrent properties, (b) (4)

[REDACTED]

Dr. Jim Tolliver of the Controlled Substance Staff stated the following in an email dated November 19, 2013, regarding this submission:

From: Tolliver, James
To: Chiapperino, Dominic; Kilgore, Elizabeth; Fields, Ellen; Calderon, Silvia N;
Suarez, Sandra; Hu, Yong; Pinto, Julia
Cc: Rappaport, Bob A; Hertz, Sharon H; Jani, Parinda
Subject: RE: Xartemis XR, clock extension etc
Date: Tuesday, November 19, 2013 1:05:49 PM

(b) (4)



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/s/

ELLEN W FIELDS
11/20/2013

BOB A RAPPAPORT
11/20/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, November 08, 2013 2:28 PM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031, Carton/Container labeling comments

Hi Kevin,

Regarding the submitted carton and container labeling for Xartemis XR, we have the following comments.

A. All Container Labels (Bottle and Unit Dose) and Carton Labeling

1. Revise the presentation of the proprietary name so it appears in title case rather than all capital letters to improve readability.
2. Remove the (b) (4), which extends from the first letter "X" and above the proprietary name, to improve readability.
3. Revise the established name to include the dosage form "oxycodone hydrochloride/acetaminophen extended release tablets".
4. Revise the font color of the strength statement from (b) (4) to black to improve readability. As presented, the light colored font on a light colored background may be difficult to read.

B. Bottle Container Labels and Carton Labeling

1. Ensure there is adequate white space between the established name and the CII designation so that the CII designation does not interfere with the readability or appear as a part of the established name statement.
2. Realign the strength statement so that its justification is aligned to the left to allow space for the next recommendation.
3. Revise the statement from "(b) (4)" to read "Swallow whole. Do not break, chew, crush, cut, dissolve, or split Xartemis XR."
4. Clarify whether you will use a secondary packaging (carton container) for the bottles and provide the carton label as necessary.

C. Unit Dose Blister Labels

1. Reduce the size of the CII designation. As presented, it is more prominent than, and may distract from, other important information, such as the proprietary and established names.
2. If space permits, revise the appearance of strength on the blister container backing to describe the milligram amount of drug per single unit to appear as follows:

XX mg/XX mg per tablet

D. Unit Dose Carton Labeling

1. Revise the appearance of the strength statement on principal display panel of the carton labeling to describe the milligram amount of drug per single unit to mitigate medication errors of wrong dose and to appear as follows:

Contents: XX mg/XX mg per tablet
100 Unit-Dose tablets

Please contact me if you have any questions.

Best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
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Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
11/08/2013

PeRC PREA Subcommittee Meeting Minutes
October 2, 2013

PeRC Members Attending:

Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno
Tom Smith
Andrew Mulberg (Did not review [REDACTED] (b)(4))
Wiley Chambers
Donna Katz
Robert “Skip” Nelson
Shrikant Pagay
Lily Mulugeta
Andrew Mosholder
Kevin Krudys
Barbara Buch
Susan McCune
Daiva Shetty
Martha Nguyen
Peter Starke
Ruthianna Davi
Gregory Reaman
Jane Inglese
William Rodriguez
George Greeley
Coleen LoCicero
Robert “Skip” Nelson
Rachel Witten
Maura O’Leary

Guests Attending:

Nichella Simms (PMHS)	Amy Taylor (PMHS)
Erica Radden (PMHS)	GT Wharton (OPT)
Courtney Suggs (OCP)	Gilbert Burckart (OCP)
Donna Snyder (PMHS)	Robert Levin (DPP)
Dionna Green (OCP)	Owen McMaster (DAIP)
Alison Rodgers (DAIP)	Ronald L. Ariagno (OPT/PMHS)
Jian Wang (OCP)	Ellen Fields (DAAAP)
Elizabeth Kilgore (DAAAP)	Dominic Chiapperino (DAAAP)
Aisar Atrakdei (DPP)	Kim Updegraff (DPP)
Hao Zhu (OCP)	Yun Xu (OCP)

Agenda

9:00	NDA	(b) (6)	[Redacted]
9:20	NDA	(b) (6)	[Redacted]
9:40	NDA	204031	Xartemis (oxycodone/acetaminophen) Deferral/Plan
	NDA	(b) (6)	[Redacted]
	NDA	(b) (6)	[Redacted]
	NDA	(b) (6)	[Redacted]

[Large redacted area covering the main body of the page]

(b) (6)

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Xartemis Deferral/Plan

- NDA 204031, Xartemis (oxycodone/acetaminophen) (b) (4) release tablets seeks marketing approval for the management of (b) (4) acute pain where the use of an opioid analgesic is appropriate.
- The supplement was received on May 28, 2013 and has a PDUFA goal date of November 28, 2013 (planned action date is November 22, 2013).
- The application triggered PREA as a new dosing regimen.
- A deferral is being requested for all pediatric patients ages birth to 17 years because the product is ready for approval in adults.
- The Agency advised the Sponsor that the pharmacokinetics (PK) and safety of COV795 must be assessed over the entire pediatric age range and efficacy must be assessed for pediatric patients under the age of 2 years to comply with PREA.
- The FDA has advised Mallinckrodt that the pediatric studies can be conducted with an age-appropriate formulation that is not required to retain the GR (gastroretentive) or PK characteristics of the adult COV795 formulation. The Agency further advised Mallinckrodt that if the age appropriate formulation developed for the PREA studies is different from the adult formulation, the PK profile of the formulation must be characterized in the adult population prior to initiating studies in pediatric patients.
- This is an extended-release opioid for acute pain as there are no other products available that are extended-release for acute pain. Efficacy will be extrapolated down to age 2.
- The Division agreed to the plan for the sponsor to conduct studies sequentially.
- The PeRC agreed to the proposed timelines for the deferred studies.

PeRC Recommendations:

- The PeRC agreed with the Division to grant a complete deferral for all pediatric patients because the product is ready for approval in adults.

Additional PeRC Recommendation/s:

- The PeRC recommends that the Division work with the sponsor to tighten the timelines for the PREA PMRs, specifically the time between when one study completes and the next protocol is submitted to the Agency.

(b) (6)

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/s/

GEORGE E GREELEY
11/06/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Wednesday, October 23, 2013 5:25 PM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031, information request and comments

Dear Kevin,

Regarding NDA 204031, we have some comments related to 505(b)(2) considerations for your application and your proposed Xartemis XR prescribing information.

1. Your annotated label references products not listed for patent certification in your application. This is not acceptable, and appropriate patent certifications must be provided.
2. In addition, an applicant may cross-reference a previously approved 505(b)(2) application for which it is the NDA holder to support approval of its new NDA, if scientifically appropriate. If the cross-referenced portions of an applicant's previously approved 505(b)(2) application involve reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or published literature (as distinguished from any cross-referenced investigations that may have been conducted by or for the applicant or for which the applicant has obtained a right of reference or use), then the new NDA should be submitted pursuant to section 505(b)(2) of the FD&C Act. An applicant's new 505(b)(2) application should identify this/these listed drug(s) as relied upon for its new 505(b)(2) application in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification/statement and notification), apply to each listed drug upon which an applicant relies.
3. You did not indicate reliance on published literature in your cover letter. However, you did reference literature in your annotated label. In order for your proposed product labeling to be approved, certain published literature references are essential, and we request confirmation that all the published literature necessary for approval has been submitted to the application. If not, then you must amend your application with all published literature necessary for approval.
4. It is not acceptable to annotate your proposed label with the statement "[REDACTED] (b) (4)," as this does not indicate whether or not your proposed labeling is based on: 1) your own submitted data; 2) data and information for which you have right of reference; 3) appropriately referenced literature; or 4) product labeling of the drug(s) you have appropriately listed for 505(b)(2) purposes.

Contact me if you have questions at this time.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
10/23/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204031

GENERAL ADVICE

Mallinckrodt Inc.
Attention: Kevin D. Healy
Associate Director Regulatory Affairs
675 McDonnell Blvd.
Hazelwood, MO 63042

Dear Mr. Healy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xartemis XR (oxycodone hydrochloride/ acetaminophen) extended-release tablets, 7.5 mg/325 mg.

We also refer to your October 4, 2013, containing your proposed IVIVR . We acknowledge the additional information provided; however it does not support your proposed IVIVR. We reiterate the no acceptability of your IVIVR. We have reviewed the referenced material and have the following comments:



Under these circumstances, you should follow the SUPAC-MR recommendations in terms of the data needed to support any future manufacturing change.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,
{See appended electronic signature page}
Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
10/21/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, October 18, 2013 4:04 PM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031 information request, REMS
Attachments: rems-and-materials-tracked-changes + fda comments 10_17_2013.docx

Dear Kevin,

Regarding NDA 204031 and your proposed REMS for Xartemis XR, we have the following comments and revised document showing tracked changes (attached) at this time and request that you submit the revised REMS and materials as amendment at your earliest convenience.

1.1 REMS DOCUMENT

Revise the header of the document to read as:

Initial REMS Approval: 07/2012
Most Recent Modification: XX/2013

1.2 FDA BLUEPRINT

1. Reapply appropriate page numbers in the right corner of the pages.
2. See attached FDA Blueprint for the Agency's comments and suggested track changes.

1.3 PRESCRIBER LETTERS 1, 2, 3

The letters must be revised to incorporate the proposed indication of acute pain for Xartemis XR.

1.4 ER/LA OPIOID ANALGESICS REMS WEBSITE

See the attached REMS Website for suggested track changes.

1.5 GENERAL COMMENTS

Resubmission Requirements and Instructions: Submit the revised proposed REMS with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single MS Word document.

1.6 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

Contact me if you have any questions at this time.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
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Office phone: (301) 796-1183
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/s/

DOMINIC CHIAPPERINO
10/18/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Friday, October 18, 2013 3:49 PM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031 information request

Dear Kevin,

Regarding the Xartemis XR NDA, we have an additional request for information at this time, as follows:

1. In Study 0182, Subject 201-155 (randomized to placebo), experienced an SAE of hypersensitivity. The subject was hospitalized and treated with diphenhydramine for the SAE of hypersensitivity but the narrative does not describe symptoms. Provide a more detailed narrative including information on specific symptoms and any additional information from the hospital report if possible.
2. In the Phase 3 Integration Set, five subjects were identified as experiencing potential withdrawal symptoms while receiving COV795. Brief narratives were provided for these subjects (204-004, 204-110, 110-023, 131-009 and 145-012). Clarify whether these withdrawal symptoms occurred after cessation of study drug.

Contact me if you have questions, otherwise we look forward to your response.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
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Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
10/18/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, October 15, 2013 9:55 AM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031, information request

Dear Kevin,

Regarding NDA 204031, we have another request for information, at your earliest convenience.

For the Phase 3 studies 0182 and 0181 and Phase 1 studies which used the to-be-marketed formulation, provide a summary table(s) by treatment received (not treatment group assigned) for subjects with elevated LFTs to include:

- Total number of subjects with LFTs $\geq 2xULN$
- Total number of subjects with LFTs $\geq 3xULN$
- Total number of subjects with LFTs $\geq 5xULN$
- Total number of subjects with LFTs $\geq 10xULN$
- Total number of subjects with total bilirubin $\geq 2xULN$
- Total number of discontinuations due to elevated LFTs

For the Phase 3 studies, provide the patient ID number for each case. The tables should clearly distinguish those subjects who received placebo only and those who received study drug.

Would it be possible for you to provide me with this information later today, at least by email? Your formal amendment with the information would be expected at your earliest convenience.

Thank you and best regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
10/15/2013



NDA 204031

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Mallinckrodt, Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

ATTENTION: Kevin Healy, PhD
Director, Regulatory Affairs

Dear Dr. Healy:

Please refer to your New Drug Application (NDA) dated May 24, 2013, received May 28, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride and Acetaminophen Extended-release Tablets, 7.5 mg/325 mg.

We refer to:

- Your correspondence, dated and received on July 18, 2013, requesting review of your proposed proprietary name, Xartemis;
- The teleconference held on August 5, 2013, between FDA and Mallinckrodt, Inc. where you were informed that a modifier should be added to convey the extended release properties of the product; and
- Your proprietary name amendment dated and received August 23, 2013.

We have completed our review of the proposed proprietary name, Xartemis XR and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your July 18, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dominic Chiapperino at 301-796-1183.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/03/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, September 24, 2013 9:58 AM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: RE: NDA 204031, information request

Hi Kevin,

We would like to amend the language we used in comment #4 in my previous email. Please substitute this version for comment 4:

4. Provide a list of all subjects with elevated hepatic function tests >2x ULN in Studies 0182 and 1081, and provide narrative for all subjects with elevated hepatic function tests $\geq 3x$ ULN (whether the subject discontinued or continued in the study), since abnormal hepatic function tests and hepatic-related AEs have been identified as AEs of special interest.

Thank you,
Dominic

From: Chiapperino, Dominic
Sent: Tuesday, September 24, 2013 9:49 AM
To: Healy, Kevin D (Kevin.Healy@mallinckrodt.com)
Subject: NDA 204031, information request

Dear Kevin,

Based on our review of NDA 204031 thus far, we have the following comments and request for additional information:

You state in Study 0182 Clinical Study Report the following:

1. "Three subjects experienced at least 1 LFT value (ALT, AST, ALP, total bilirubin, or direct bilirubin) that was out of reference range and assessed by the investigator as AEs (Subjects 201-078, 202-047, 204-142)" and provided a table which included subject 201-178, as shown below:

Table 12.4.2.3-1: Clinical Laboratory Results for Subjects with AEs Correlated with Abnormal LFTs

Subject (Treatment)	Laboratory Test Standard Range	Baseline	Double	OLE Phase	OLE Phase	OLE Phase	OLE Phase	
			Blind Day 2 \pm 1	Day 7 \pm 1	Day 14 \pm 1 Unscheduled Visit 1	Day 14 \pm 1 Unscheduled Visit 2	Day > 15 Unscheduled Visit 1	Day > 15 Unscheduled Visit 2
201-178 (COV795*)	^a ALT 6-34 U/L	11 U/L	9 U/L	High			15 U/L Day 20	
	^b ALP 35-123 U/L	109 U/L	95 U/L	High 129 U/L (1.0X)			110 U/L Day 20	
	^b AST 9-34 U/L	19 U/L	17 U/L	High 75 U/L (2.2X)			18 U/L Day 20	
	Bilirubin 3-21 μ mol/L	15 μ mol/L	12 μ mol/L	10 μ mol/L			9 μ mol/L Day 20	
	Direct Bilirubin 0-7 μ mol/L	3 μ mol/L	3 μ mol/L	2 μ mol/L			2 μ mol/L Day 20	

- Clarify the following regarding the above:
 - Is there a typo in the table and should the Subject ID number be 201-078, not 201-178 as written in the table?
 - Provide the location in the submission for the narrative for subject 201-078, or if no narrative was submitted, provide a narrative for this subject describing the course of the adverse event in relation to the dosing of the study drug.

2. Two of the 6 subjects (202-047, 204-037) had an ALT and/or AST value > 5 times ULN during the study. Subject 202-047 had a maximum ALT of 6.5 times ULN and AST of 7.5 times ULN in the OLE phase on Day 8. Maximum ALP was 1.2 times ULN in the OLE phase on Day 8. Total bilirubin was normal. This subject was discontinued from the study secondary to increased hepatic enzymes. All LFT values returned to within reference range by Day 21 visit. Subject 204-037 had a maximum ALT of 13 times ULN, AST 7 times ULN, and ALP 3.2 times ULN in the OLE phase on Day 7. Total bilirubin was normal. All LFT values returned to within reference range after Day 15.
- Clarify the following regarding the above:
 - Provide a narrative for subject 204-037 describing the course of the adverse event in relation to dosing of study drug.
3. Identify the hepatic function laboratory criteria used to determine whether a subject with abnormal hepatic laboratory values continued or was discontinued from Studies 0182 and 0181.
 4. Provide narratives for all subjects with elevated hepatic function tests $\geq 2x$ ULN in Studies 0182 and 1081, whether the subject discontinued or continued in the study, since abnormal hepatic function tests and hepatic-related AEs have been identified as AEs of special interest.

Please provide this information with a goal of COB September 30, 2013 or as soon as feasibly possible. Contact me if you have any questions.

Thank you and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
09/24/2013



NDA 204031

INFORMATION REQUEST

Mallinckrodt Inc.
Attention: Kevin D. Healy
Associate Director Regulatory Affairs
675 McDonnell Blvd.
Hazelwood, MO 63042

Dear Mr. Healy:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Xartemis XR (oxycodone hydrochloride/acetaminophen) extended-release tablets, 7.5 mg/325 mg.

We have the following comments and information requests. We request a written response by **Friday, October 4, 2013**, in order to continue our evaluation of your NDA.

1. Provide solubility differences among the crystalline forms of oxycodone hydrochloride and acetaminophen as a function of pH.
2. We recognize your efforts in the development of an in vitro in vivo relationship (IVIVR) for your proposed product. However, we have found the following deficiencies in your simulation approach that render your proposed IVIVR unacceptable. (b)(4)

[Redacted text block]

3. The provided dissolution data do not support the selection of (b)(4) hours as the last sampling time point and, therefore, this time point is not acceptable. Implement the following dissolution acceptance criteria for your proposed product and provide the updated specification tables for your product at batch release and on stability with the revised dissolution criteria.

For Acetaminophen			
	Target	Minimum	Maximum
0.5 hours	(b) (4)		
2 hours			
4 hours			
6 hours			

For Oxycodone			
	Target	Minimum	Maximum
0.5 hours	(b) (4)		
2 hours			
4 hours			
6 hours			

4. Update the acetaminophen drug substance specification to include the Identification Test B in accordance with the current acetaminophen monograph in the USP 36. The Test B states that "The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay."
5. Include particle size distribution in the specifications for both oxycodone HCl and acetaminophen drug substances. Controlling particle size is important for ensuring the content uniformity of oxycodone HCl and the acceptable release of acetaminophen from the product. It is also important to control the particle size when you change the suppliers of the drug substances. The particle size specifications should be justified using the clinical batch data. Wider ranges than those tested in pivotal clinical trials should be supported with BA/BE data or dissolution profiles comparisons (f2 testing).
6. Clarify whether the quantities of the IR and ER tablet (b) (4) in the Table 3.2.P.2.3-1. Make corrections if necessary.
7. Provide data to justify the process parameter set points and ranges proposed for the commercial scale manufacturing of the drug product. This can include:
 - a. Commercial scale batch data to demonstrate verification of the set points/ranges
 - b. Submission of relevant scale up correlations to justify the proposed commercial scale set points/ranges.
 - c. Other justifications as appropriate.
8. Per ICH Q1A, revise your post-approval drug product stability commitment to include placing the first three production batches on accelerated stability studies for 6 months, in addition to the long-term stability studies.
9. Comparability protocol:
 - a. Include drug substance particle size analysis.
 - b. Revise the reporting category to prior-approval supplement (PAS) as this is a high risk opioid product.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

DANAE D CHRISTODOULOU
09/20/2013
Signed for Prasad Peri

MEMORANDUM of TELECONFERENCE

MEETING DATE: August 5, 2013
TIME: 10:30 am to 11:00 am EDT
LOCATION: Conference room 4266, Building 22
APPLICATION: IND 104702 and NDA 204031
DRUG NAME: Xartemis (Oxycodone Hydrochloride/Acetaminophen) (b)(4) -
Release Tablets
TYPE OF MEETING: Teleconference

MEETING CHAIRS: Jamie Wilkins Parker, Team Leader, DMEPA
Vaishali Jarral, OSE Project Management

FDA ATTENDEES: Vicky Borders-Hemphill, Safety Evaluator, DMEPA
Darrell Jenkins, OSE Chief Project Management Staff

SPONSOR ATTENDEES: Kevin Healy, Regulatory Affairs
Alan Blumberg, Regulatory Affairs
Mark Mannebach, Regulatory Affairs
Mike Wessler, Commercial Marketing

BACKGROUND:

Mallinckrodt Inc. (Mallinckrodt) submitted original NDA 204031 on May 24, 2013 for MNK795 (oxycodone hydrochloride (OC) and acetaminophen (APAP) (b)(4) -release tablets). The investigational drug number related to this product is IND 104702. Mallinckrodt Inc. has submitted a request for proprietary name review for “Xartemis” to both IND 104,702 (OSE PDUFA date: August 13, 2013) and to NDA 204031 (OSE PDUFA date October 16, 2013).

MEETING OBJECTIVES:

The purpose of the call was to let Sponsor know that DMEPA has completed their preliminary review of the name, and finds it unacceptable because of the lack of a modifier such as ER or XR to convey the extended release properties of Xartemis.

DMEPA CONCERNS WITH THE PROPOSED NAME:

The proposed product has overlapping strength and frequency of administration with existing immediate-release products and our concerns were conveyed at the December 2012 Pre-NDA meeting. While we support the use of a comprehensive educational and labeling strategic approach and the use of a unique proprietary name, these strategies should not be used exclusively to mitigate the potential for medication errors. Postmarketing surveillance of extended-release products approved without a modifier in the proprietary name whose strengths overlap with the immediate-release product strengths has revealed wrong frequency of administration and wrong technique (crushing, chewing, dissolving, etc.) medication errors. These errors have been seen with products which have unique proprietary names and labeling which highlights the extended-release properties of the product (Exalgo and hydromorphone for example).

Therefore, while the root name, Xartemis is conditionally acceptable, to mitigate the risk of medication errors that may result in wrong frequency and wrong dose errors we recommend the use of a modifier such as ER or XR to convey the extended-release properties of Xartemis.

REGULATORY OPTIONS:

Following two options were present to the sponsor:

- 1) Withdraw the request for proprietary name review submission from the IND and amend the request for proprietary name review in the NDA.
- 2) Receive an unacceptable letter for both the IND and the NDA.

DISCUSSION:

Mallinckrodt agreed to regulatory option #1, and committed to submit a withdrawal letter to IND. The applicant further agreed to submit the root name, Xartemis, with a modifier appended to the name as an amendment to the Request for Proprietary Name Review under NDA 204031.

Applicant proposed using (b)(4) as a modifier, but their proposal was rejected as using (b)(4) as a modifier is not acceptable. Applicant requested additional information regarding this matter and FDA committed to provide this information to them shortly.

ACTION ITEMS:

- 1) Mallinckrodt will submit a “Withdrawal of Request for Proprietary Name Review” request to IND 104702 by COB August 7, 2013.
- 2) Mallinckrodt will also submit the root name, Xartemis, with a modifier appended to the name as an amendment to the Request for Proprietary Name Review originally submitted to NDA 204031 on July 18, 2013.
- 3) FDA will provide additional information to Mallinckrodt regarding FDA’s policy for using (b)(4) as a modifier appended to drug names.

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/s/

VAISHALI JARRAL
08/15/2013

Jani, Parinda

From: Jani, Parinda
Sent: Sunday, August 11, 2013 10:00 PM
To: 'kevin.healy@mallinckrodt.com'; 'jennifer.weidman@mallinckrodt.com'
Cc: Chiapperino, Dominic
Subject: NDA 204031/comment regarding proprietary name

Dear Kevin and Jennifer:

The Division of Medication Error Prevention and Analysis (DMEPA) and the Labeling and Nomenclature Committee (LNC) have provided the following comment regarding your proposed proprietary name Xartemis (oxycodone hydrochloride/acetaminophen) (b)(4)-release tablets, 7.5 mg/325 mg..

The proposed modifier (b)(4) is not an approved dosage form. For established names, the only acceptable term is 'extended-release.' The following information comes from the USP Nomenclature Guidelines:

[Extended-Release— Extended-release products are formulated in such a manner as to make the drug substance available over an extended period of time following ingestion. Expressions such as "prolonged-release", "repeat-action", "controlled-release", "sustained-release", and their corresponding acronyms should not be used to describe such dosage forms. The term "extended-release" is used for compendial nomenclature.](#)

Please revise the established name from “Oxycodone hydrochloride and acetaminophen (b)(4)-release tablet” to “Oxycodone hydrochloride and acetaminophen extended-release tablet”.

Sincerely,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232

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/s/

PARINDA JANI
08/11/2013



NDA 204031

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Kevin D. Healy
Associate Director Regulatory Affairs

Dear Mr. Healy:

Please refer to your New Drug Application (NDA) dated May 24, 2013, received May 28, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xartemis (oxycodone hydrochloride/acetaminophen) (b) (4)-release tablets, 7.5 mg/325 mg.

We also refer to your amendment dated July 18, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is November 28, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 7, 2013.

During our filing review of your application, we identified the following potential review issues:

Product Quality

1. The drug product release specifications currently do not include testing, in accordance with USP 1217, for tablet hardness.

2. Your submission currently does not appear to address whether or how large the intact tablet will swell and whether it becomes sticky in water and in simulated gastric fluids over time. This information may help assess the risk of GI obstruction due to the tablet.
3. Your submission currently does not contain adequate data to characterize the dissolution profile of the drug product in order to support the selection of the proposed dissolution acceptance criteria (i.e., specification-sampling time points and values) for your proposed drug product specifications.

Biostatistics

4. Your submission does not appear to include subgroup analyses by age, gender, or race for your efficacy Study COV15000182US.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Provide revised drug product specifications that include a suitable test of tablet hardness, in accordance with USP 1217.
2. Provide data that 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.
3. 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.
4. Either specify the location in the current submission of the subgroup analyses by age, gender, and race in your efficacy Study COV15000182US or provide these analyses.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Some headings in the Highlights (HL) section do not have any white space to separate them from preceding paragraphs. White space must be present before each major heading in HL.
2. In the Boxed Warning section of HL, some text is not in bold font. All text in this section should be bold font.

3. Since oxycodone is in the well-known pharmacologic class of opioid analgesics, this should be reflected in the Indications and Usage section of HL. For example, “XARTEMIS is a combination of oxycodone, an opioid agonist, and acetaminophen, and is indicated for...”
4. The Boxed Warning title in the Table of Contents (TOC) is not identical to the Boxed Warning title in HL and in Full Prescribing Information, and the TOC title should be revised.

We request that you resubmit labeling that addresses these issues by August 15, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
07/25/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Tuesday, June 25, 2013 3:59 PM
To: Healy, Kevin D
Subject: NDA 204031, information request

Hi Kevin,

Referring to your NDA 204031 for Xartemis, we note that your financial disclosure information in Section 1.3 of the NDA submission differs from the Agency's Office of Scientific Investigations (OSI) risk-based model tool for site selection. In the tool dataset, there were substantial sums reported for clinical investigators (CIs). However, in the submission, no amounts were reported for the CIs.

Explain this discrepancy and, if applicable, resubmit a corrected version of the financial disclosure document.

Thank you, and kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
FDA, Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

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/s/

DOMINIC CHIAPPERINO
06/25/2013



NDA 204031

NDA ACKNOWLEDGMENT

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Kevin D. Healy
Associate Director Regulatory Affairs

Dear Mr. Healy:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xartemis (oxycodone hydrochloride/acetaminophen) (b)(4)-
release tablets, 7.5 mg/325 mg

Date of Application: May 24, 2013

Date of Receipt: May 28, 2013

Our Reference Number: NDA 204031

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 27, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

DOMINIC CHIAPPERINO

05/29/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 104702

MEETING MINUTES

Mallinckrodt, Inc.
One Gateway Building, Suite 120
2100 Gateway Centre Blvd.
Morrisville, NC 27560

Attention: Kevin D. Healy, Ph.D., R.A.C.
Associate Director, Regulatory Affairs

Dear Dr. Healy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for COV795 (oxycodone hydrochloride and acetaminophen (b) (4) extended-release tablets).

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2012. The purpose of the meeting was to discuss the requirements for your planned NDA for COV795.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 13, 2012
Meeting Location: 10906 New Hampshire Avenue, Bldg 22, Room 1311; Silver Spring, MD 20906

Application Number: IND 104702
Product Name: COV795 (Oxycodone Hydrochloride/Acetaminophen (b) (4) Extended-Release Tablets)

Indication: Management of (b) (4) acute pain
Sponsor/Applicant Name: Mallinckrodt, Inc.

Meeting Chair: Ellen Fields, M.D.
Meeting Recorder: Lisa Basham, M.S.

FDA ATTENDEES:

Bob A. Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Sharon Hertz, M.D.	Deputy Division Director, DAAAP
Ellen Fields, M.D., M.P.H.	Clinical Team Leader; DAAAP
Prasad Peri, Ph.D.	Branch Chief, Division III, Branch VIII, Office of New Drug Quality Assessment (ONDQA)
Dionne Price, Ph.D.	Team Lead, Division of Biometrics II (DBII), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAAP
Yun Xu, Ph.D.	Team Leader, Clinical Pharmacology, Division of Clinical Pharmacology II (DCP2)
Jin Chen, M.D., Ph.D.	Clinical Reviewer, DAAAP
Danae Christodoulou, Ph.D.	CMC Lead, ONDQA
Craig Bertha, Ph.D.	Product Quality Reviewer, ONDQA
David Petullo, Ph.D.	Statistics Reviewer, DBII, OB, OTS

James Tolliver, Ph.D. Mark Liberatore, Pharm.D.	Pharmacologist, Controlled Substance Staff (CSS) Safety Regulatory Project Manager, Office of Safety and Epidemiology (OSE)
Reema Mehta, Pharm.D., M.P.H. Danielle J. Smith, Pharm.D., M.S.	Team Leader, Division of Risk Management, OSE Drug Risk Management Analyst, Division of Risk Management, OSE
Elizabeth M. Maloney, M.S., Dr.P.H. Jamie Wilkins-Parker, Pharm. D.	Epidemiologist; Division of Epidemiology II; OSE Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology, OSE
Vicky Borders-Hemphill, Pharm.D. Vipul Dholakia, Ph.D.	Safety Evaluator, DMEPA, OSE Interdisciplinary Scientist - Chemist Office of Manufacturing and Product Quality Office of Compliance
Lisa Basham, M.S.	Senior Regulatory Health Project Manager, DAAAP

SPONSOR ATTENDEES:

Michael Giuliani, M.D. Keith Moore, Pharm.D. Becky Bates, M.S. Mark Mannebach, Ph.D. Kevin Healy, Ph.D. Ralph Heasley, Ph.D.	Clinical Clinical Consultant Biostatistics Regulatory Affairs Regulatory Affairs Chemistry, Manufacturing, and Controls
---	--

BACKGROUND

Mallinckrodt's proposed product is COV795 (oxycodone hydrochloride [OC] and acetaminophen (b) (4) extended-release tablets), 7.5 mg OC/325 mg acetaminophen, for the management of (b) (4) acute pain. This drug formulation utilizes Depomed AcuForm[®] gastroretentive (GR) drug delivery technology. The bilayer formulation includes an immediate-release (IR) layer and an extended-release (ER) layer intended, respectively, to provide immediate release of each drug for treatment of initial acute pain and extended release of each drug to manage pain for up to 12 hours. The formulation may also confer some abuse-resistant characteristics to the product (b) (4).

The original IND for COV795 was submitted on May 19, 2010. Written responses were provided on December 7, 2011, in lieu of an End-of-Phase 1 (EOP1) meeting requested on July 12, 2011. A June 8, 2012 Type A meeting request pertaining to the statistical analysis plan for Phase 3 Efficacy Study 0182 was granted written responses, dated August 14, 2012. Interactions related to a parallel drug development program (IND 109,246; COV155, HB/acetaminophen) informed this program.

The Sponsor proposes a 505(b)(2) NDA relying on the Agency's previous findings of safety and efficacy for Roxicodone (NDA 021011, 15 mg oxycodone) and Ultracet (NDA 021123, 37.5 mg tramadol/325 mg acetaminophen). Two comparative bioavailability studies were conducted

using these comparator drugs: Study 0256 (single dose) and Study 0255 (multiple dose). The Phase 3 program consisted of a double-blind, placebo-controlled efficacy trial (Study 0182) and an open-label safety trial (Study 0181). Additionally, COV795 has been evaluated in a human abuse liability trial (Study 0244).

Mallinckrodt Inc. submitted a request for a Pre-NDA meeting on September 14, 2012. The meeting was granted and the meeting package arrived on November 1, 2012. On December 10, 2012, we provided preliminary responses to the Sponsor's questions. On December 12, 2012, Mallinckrodt identified the items they wish to discuss and provided clarification comments and questions regarding some of our preliminary responses. For ease of reference, the Sponsor's questions are reproduced below in italicized text, followed by our preliminary responses in bold text. The Sponsor's pre-meeting response follows in Arial font. Discussion during the meeting is identified as such and shown in normal text.

DISCUSSION

Regulatory Questions

Question 1: Proposed USPI and Labeling

Given that COV795 contains the same APIs and has some overlap in indication with IR OC/APAP in clinical practice, does the Agency agree that physicians may benefit from understanding the relative PK profiles, and that it may be appropriate to include a graphical PK comparison between COV795 and IR OC/APAP in the proposed label?

FDA Response:

The pharmacokinetic (PK) data presented in a label is informative to prescribers. However, selection of the appropriate comparative PK data for labeling will be determined during review of the NDA. As an ANDA, Percocet (7.5/325 mg oxycodone/acetaminophen) is not acceptable for use as a reference for the Agency's prior findings of efficacy or safety. You have not conducted any studies comparing the efficacy or safety of COV795 with Percocet. Therefore, it is unclear that inclusion of PK data comparing COV795 and Percocet is appropriate for inclusion in the labeling of COV795.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt would appreciate further discussing the most appropriate comparator for COV795 labeling. We agree with the Agency position that including comparative PK data for this relatively complex dose formulation (bi-layer dose form with 2 APIs) will be informative to prescribers, and acknowledge that studies comparing the efficacy of COV795 with Percocet have not been conducted. However, Mallinckrodt has included a Percocet reference arm in the comparative bioavailability studies that included the LDs Roxicodone and Ultracet (Study 0256 [single dose] and Study 0255 [multiple dose]), and believes that the overlap in the APIs and indication with IR OC/APAP will result in prescribers utilizing COV795 as a treatment option in place of Percocet more often than in place of the LDs.

Further, a PK comparison between COV795 and IR OC/APAP may help physicians better understand COV795 and reduce medication errors (see the "Additional Comment from the Division of Medication Error Prevention and Analysis").

DISCUSSION:

(b) (4)



DISCUSSION: No discussion necessary.

B. Mallinckrodt's preliminary intention for the pediatric plan is to subcategorize pediatric patients into 3 cohorts for trial protocol development and study execution (i.e., an adolescent patient cohort (ages 12-17), children patient cohort (ages 2 to 11) and the infant patient cohort (age < 2). Pediatric studies would be conducted sequentially, beginning with the adolescent population. Mallinckrodt believes the COV795 IR/ER bilayer formulation is age-appropriate for the 12 to 17 year-old pediatric patients, based upon maturation of the metabolic pathways for OC and APAP in this age population, their ability to swallow the tablet, and comparable dosing requirements to the adult patient cohort. Based upon an NDA filing containing the Pediatric Plan and initial PREA study protocol in the second quarter of 2013, Mallinckrodt projects that the first PREA study would commence in 2014. Distinct age-appropriate formulations will need to be developed for the younger pediatric patients. Does the Agency agree with submitting a pediatric plan with the NDA, and the general approach outlined above?

FDA Response:

We encourage you to submit your pediatric plan as soon as possible, however, at this time it is acceptable to submit it with your NDA. Beginning in January 2013, sponsors must submit a Pediatric Study Plan (PSP) within 60 days of the scheduled End-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach), any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov

Your proposal to study three sequential age-cohorts appears reasonable.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments.

(b) (4)

(b) (4)

(b) (4)

Question 3 – Presentation of Abuse Related Data; Proposal for Scheduling Consistent with the January 2010 Draft Guidance “Assessment of the Abuse Potential of Drugs,” the COV795 NDA will include a description and analysis of studies related to the abuse of the drug and a proposal for scheduling. Based upon the inclusion of OC as an API in COV795, Mallinckrodt will request a Schedule II designation for the drug product. Several in vitro studies and a human abuse liability trial (Study 0244) have been conducted in order to evaluate the tamper-resistance properties and relative abuse potential of COV795. In vitro dissolution experiments conducted with a range of ethanol concentrations have established that alcohol-mediated dose dumping does not occur in vitro (see CMC Question 18). The Human Abuse Liability trial (Study 0244) was previously submitted for Agency review, and Mallinckrodt incorporated recommendations from the Controlled Substances Staff and DAAAP into the study protocol (Protocol Amendment and Efficacy Information Amendment, SN 0032). Mallinckrodt intends to report the Study 0244 results in the NDA (eCTD Module 5.3.5.4). Mallinckrodt would appreciate specific feedback on the presentation of in vitro and clinical trial data relative to abuse potential assessments in the NDA.

- A. *The COV795 abuse potential assessment will include the general topics suggested in the January 2010 Draft Guidance. Regarding the clinical trial data relative to abuse and dependence potential, the Phase 3 clinical study reports will tabulate the abuse, misuse, noncompliance, and diversion cases, and provide complete information on study activity that may be abuse-related. Are there specific data presentations or additional assessments specific to COV795 abuse potential that the Agency would value reporting upon in the NDA?*

FDA Response:

All information pertaining to the abuse potential assessment of COV795 should be available in the NDA as specified in the January 2010 draft guidance to industry *Assessment of the Abuse Potential of Drugs*.

All cases from Phase 3 clinical studies of actual or suspected abuse, misuse, noncompliance, and diversion should be summarized in tabular form with narratives. Clearly state the criteria used to identify each of these cases. Case report forms providing complete information on instances of abuse, misuse, noncompliance, and diversion should be submitted in the NDA in such a way as to be easily identified and readily retrievable electronically. Consider providing an electronic link between the summary table and the case report forms.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion required at this time.

DISCUSSION: No discussion necessary.

- B. *The integrated summary of safety will include a combined analysis of the adverse event (AE) and safety profile* (b) (4)

[Redacted]

FDA Response:

Yes, this approach is acceptable. (b) (4)

[Redacted]

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Question 4 – Risk Evaluation and Mitigation Strategy (REMS)/Medical Guide

COV795 is a multilayer IR/ER designed to provide immediate (ie, within 1 hour) relief for acute pain and also sustained analgesia for up to 12 hours. The low doses of the COV795 combination opioid product (7.5 mg OC/325 mg APAP) confer relative safety in comparison to many of the ER opioid products that contain significantly higher levels of opiates, are indicated for chronic pain, and are subject to the long-acting opioid class-wide REMS. (b) (4)

(b) (4)
[Redacted text block]

Given the composition of COV795 and acute pain indication, Mallinckrodt does not believe that this product should be subject to the long acting opioid class-wide REMS. Mallinckrodt intends to focus on ensuring safe use of COV795 through appropriate labeling, including a Medication guide, and customized physician education materials (b) (4)

[Redacted text block]

Does the Agency agree with this approach?

FDA Response:

Based on the information available at this time, specifically that your formulation contains extended-release oxycodone, a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. Therefore, we refer you to the approved REMS for extended-release and long acting-opioids (Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>). Submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the NDA, will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comment that a REMS will be necessary to ensure the benefits of COV795 outweigh the risks. Notably, the products in the extended-release and long acting-opioids class-wide REMS (ER/LA REMS) program are all approved for the treatment of chronic pain (used to treat moderate to severe around-the-clock pain). Given the low dose of COV795 ((b) (4) OC (b) (4) APAP Q12h) and the acute pain indication, there are elements of the ER/LA REMS program, which is in place for long-acting opiates approved for the management of chronic pain, that are less applicable to COV795 (example from the FDA Blueprint for Prescriber Education: "Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.").
Mallinckrodt would appreciate discussing with the Agency the suitability of the ER/LA REMS program for COV795 and developing the most

appropriate risk management program. What recommendations would the Agency have for the development of a REMS appropriate for an acute pain drug such as COV795? Does the Agency believe that a REMS containing similar information to the ER/LA REMS is appropriate for COV795? Will the Agency be willing to review the COV795 REMS early in the NDA review cycle and work with Mallinckrodt to ensure the REMS is approvable prior to the PDUFA date?

DISCUSSION:

The Agency reiterated that this product is appropriate for the ER/LA opioid class-wide REMS. The Sponsor expressed concern that the REMS review might hold up the approval of the NDA. The Agency reassured the Sponsor that, because the ER/LA class-wide REMS is already approved, the approval of this drug would require only a modification to that REMS. This should dramatically reduce the time needed to review the REMS.

Any product-specific information should be included in the relevant sections of the REMS. For example, the FDA Educational Blueprint and the Medication Guide (MG) would include information specific to their product. The proposed MG should mirror the label and utilize the one-page format of the MGs under the ER/LA opioid class-wide REMS. These may potentially be the only changes to the ER/LA opioid class-wide REMS required for COV795.

The Sponsor asked whether an Advisory Committee meeting would be needed for this product. The Agency responded that it is unlikely, however, the official decision will be made at the beginning of the NDA review process. The Agency asked whether Mallinckrodt intends to request Priority Review for the COV795 NDA. The Sponsor responded affirmatively. The Agency commented that, under a Priority Review, the determination as to whether an Advisory Committee meeting is necessary would be made within 30 days of submission. Therefore, the Sponsor would be notified approximately 1 month after filing.

Question 5 – Priority Review

The FDA has noted in several public presentations that the abuse of prescription opioid drug products is a significant public health concern and has encouraged the development of abuse-deterrent formulations. COV795 has been formulated as a low-dose opioid/APAP (7.5 mg OC/325 mg APAP) combination product with abuse-deterrent properties. The functional excipients in the formulation (i.e., polyethylene oxide) introduce physiochemical barriers to common forms of abuse (b) (4) Labs Report, Section 3.2.P.1, SN 0025), and the inclusion of APAP in the formulation may reduce the abuse potential by illicit routes of administration, particularly intravenous or intranasal administration (Budman 2009; Ball 2008).

(b) (4)
[Redacted text block]

Additionally, the Agency has expressed concerns about the potential for hepatic toxicity with APAP-containing products. At the maximum recommended COV795 dosage level of 4 tablets per day, the total APAP dose is only 1,300 mg APAP/day, and thus there is reduced potential for hepatic toxicity associated with APAP overdose (> 4,000 mg/day). COV795 is the first combination (b) (4) formulation with tamper resistant features designed for acute use; because of the medical need for opioid analgesic products that deter misuse and abuse, Mallinckrodt intends to request a Priority Review status for the upcoming NDA submission.

Does the Agency agree that these features could warrant a priority review?

FDA Response:

Yes, this product may qualify for Priority Review because of its intended abuse-deterrent features. We disagree with your (b) (4) claim for this product.

(b) (4)

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion required at this time.

DISCUSSION: No discussion necessary.

Question 6 – eCTD Submission Plan

Mallinckrodt intends to submit a 505(b)(2) for COV795 early in the 2nd quarter of 2013. As established in EOP1 correspondence with the Agency, Mallinckrodt intends to cite Roxicodone (NDA 021011) and Ultracet (NDA 021123) as LDs to support the safety and efficacy of COV795.

- A. *Given that the COV795 development plan consisted of a single efficacy study (Study 0182), Mallinckrodt intends to submit a Clinical Summary of Efficacy (CSE) in Module 2.7.3 that includes a discussion of key study design considerations, support for the COV795 dosing regimen, a brief comparison with other drugs, and a summary of the clinical pharmacology information that supports the COV795 efficacy observed in clinical evaluation. Because there will not be integrated efficacy assessments, Mallinckrodt intends to cross-reference the efficacy tables, listings, and figures from the Study 0182 CSR that will be presented in Module 5.3.5.1. Does the Agency agree with this approach? Are there additional areas of critical significance that should be addressed in the CSE?*

FDA Response:

Yes, we agree with your approach to use CSE in Module 2.7.3 by cross-linking to Study 0182 CSR in Module 5.3.5.1

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments to Questions 6 A, B, C, and D; no discussion required at this time.

DISCUSSION: No discussion necessary.

- B. A complete Integrated Summary of Safety (ISS) will be presented in Module 5.3.5.3 and a Clinical Summary of Safety (CSS) will be presented in Module 2.7.4 (see Clinical Question 8 for additional information regarding the proposed ISS contents). However, given that there is only a single efficacy trial in the COV795 program, Mallinckrodt believes it would be appropriate for the Integrated Summary of Efficacy (ISE) to simply consist of a link to the CSE in Module 2.7.3 (i.e., the narrative portion of the ISE and CSE would be identical). Does the Agency agree with this approach?***

FDA Response:

Yes, we agree with your approach to use the CSE as the ISE by cross-linking between the two modules.

DISCUSSION: No discussion necessary.

- C. All of the clinical studies of COV795 will have been conducted under IND 104,702, and the clinical study reports (CSRs) will be filed to the IND. These CSRs have not included SAS transport datasets or define XML files; those materials will be submitted with the CSRs in the NDA submission. Does the Agency agree with this approach, or have any additional advice regarding submission of clinical datasets?***

FDA Response:

Yes, we agree with your approach to submit CSRs with datasets to the NDA but not to the IND.

DISCUSSION: No discussion necessary.

- D. The NDA submission cover letter will include a reviewer's guide with electronic Common Technical Document (eCTD) locations and links to key documents in the dossier, and a listing of all clinical trial sites and their contact information. Are there any additional documents or assessments that the Agency needs in order to facilitate an efficient review process?***

FDA Response:

Yes, we agree with your proposed links to key documents in the cover letter and have no additional comments.

DISCUSSION: No discussion necessary.

APPEARS THIS WAY ON ORIGINAL

Clinical Questions

Question 7 – Phase 3 Pivotal Efficacy Study 0182

Data from the randomized, double-blind, placebo-controlled Phase 3 efficacy study will be presented in the NDA per the SAP; the primary analyses and SAP have been reviewed by the Agency and commented upon in previous correspondence (Type A meeting request, Module 1.6.1, SN 0031; Mallinckrodt response to Agencies written responses, Module 1.11.3, SN 0038; Final Study 0182 SAP, dated 12 Sept 2012, Section 5.3.5.1). Study 0182 successfully demonstrated efficacy of COV795, as the COV795 treatment was statistically significant compared to the placebo comparator for the primary endpoint (including all conducted sensitivity analyses) and all secondary endpoints. Top-line results from Study 0182, including demographics, the primary endpoint with sensitivity analyses, and TEAEs during the double-blind period, are provided in Appendix 1.

Based upon the preliminary Study 0182 results presented in Appendix 1, the additional clinical program results that will be provided in the NDA, and the lack of any unexpected safety findings of significant concern in the COV795 clinical program, Mallinckrodt believes that the safety and efficacy of COV795 has been established. While understanding that a full review of the data to be provided in the NDA is necessary, Mallinckrodt seeks Agency concurrence that Study 0182 and accompanying analyses will be sufficient, in principle, to support the indication of (b) (4) acute pain. Does the Agency agree, that on face value, the data should allow the thorough review of the NDA that is necessary to reach a positive outcome?

FDA Response:

On face, the design of the Phase 3 Study 0182 and the top-line results submitted in the meeting package appear to provide support for the efficacy of COV795 for the treatment of acute pain. While the size of the safety database appears adequate, you have not provided specific numbers of patients exposed to COV795 for at least 10 days. If these numbers meet the requirements specified during the EOP1 meeting (total of 400 subjects exposed, at least 250 exposed to 2 tablets every 12 hours for at least 10 days), then, barring any unexpected safety findings, from a clinical perspective, your NDA appears adequate for filing. However, it is premature to comment on the approvability of COV795 for the proposed indication. This decision will be made following review of the NDA.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt would like to clarify that the Phase 3 safety database includes significantly more than 400 subjects exposed to COV795. In the Phase 3 efficacy Study 0182, 166 subjects were in the COV795 blinded safety population, and an additional 69 subjects from the placebo group entered the open-label dosing period. The Phase 3 open-label Study 0181 included a safety population of 376 subjects, with 303 subjects exposed for ≥10 days.

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Question 8 – Integration Strategy

The COV795 clinical development program consisted of 12 Phase 1 studies and 2 Phase 3 studies (COV15000181, an open-label safety study, and COV15000182, a randomized, double-blind safety and efficacy program). The statistical analysis plan for the planned ISS is included in Section 5.3.5.3 of this submission; a high level overview is provided below.

For the integrated safety summaries, Mallinckrodt believes that it is most appropriate to focus on the 10 studies conducted with the intended commercial dose regimen of 15 mg OC/650 mg APAP (including studies of 1 tablet 15 mg OC/650 mg APAP tablet and studies with 2 tablets 7.5 mg OC/325 mg APAP). Five integration summary sets will be evaluated:

- *Phase 1 and Phase 3*
- *Phase 3*
- *Phase 1*
- *Phase 1 Single-dose*
- *Phase 1 Multiple-dose*

The following endpoints will be used to assess the safety of COV795 for all integration sets:

- *Disposition*
- *Demographics*
- *Study Drug Exposure*
- *AEs*
- *Laboratory Assessments*
- *Electrocardiogram (ECG) Results*
- *Vital Signs and Pulse Oximetry*

Descriptive statistics will be used to summarize age, sex, race, ethnicity, weight, height, and body mass index measurements for each of the 5 integration sets, separately. The summary of the Phase 3 integration set will be reported for all subjects combined, and by the following treatment groups: COV795-15 mg OC/650 mg APAP, COV795 < 5 days, COV795 5 to < 10 days, COV795 ≥ 10 days, and Placebo. The summary of all other integration sets will be reported for all subjects combined.

A summary of all treatment-emergent adverse events (TEAEs) will be provided for each of the 5 integration sets. In addition, for the Phase 1 and the Phase 3 integration sets the following summary tables will be provided:

- *TEAEs by maximum severity*
- *Related TEAEs*
- *AEs leading to discontinuation*
- *TEAEs by age*

- *TEAEs by sex*
- *TEAEs by race*
- *TEAEs of special interest*

All serious adverse events (SAEs) and all related AEs will be summarized for the Phase 3 integration set only. No SAEs were reported in any of the Phase 1 studies.

- A. *Does the Agency agree that Mallinckrodt's proposed subpopulations are appropriate (necessary and sufficient) for the integrated analyses? Are there additional subpopulations that the Division would like to see analyzed in the upcoming NDA?*

FDA Response:

Overall, the ISS plan appears reasonable. In addition to the proposed subpopulations, for the Phase 3 trials, provide safety data for open-label and double-blind studies.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt appreciates the Agency concurrence with the ISS plan and will integrate the Phase 3 data as described in the ISS plan. The ISS will also contain links to the Phase 3 open label (Study 0181) and double-blind (Study 0182) Clinical Study Reports (CSRs), which will be included in the NDA. Mallinckrodt would like to further discuss the Agency expectation for providing the safety data for the open-label and double blind studies. Does linking from the ISS to the Phase 3 CSRs meet Agency expectations, or would the Agency also desire the Phase 3 data to be independently presented in the ISS? If the Phase 3 data is to be independently presented in the ISS, would the Agency like to see in-text tables summarizing the key safety presentations?

DISCUSSION:

The Sponsor stated that they will integrate the Phase 3 data as described in the ISS SAP, and asked for clarification on presentation of these Phase 3 data. The Agency stated that the ISS need only contain tables of the integrated data. The tables can contain links back to the Phase 3 study reports in order to reference data tables from the individual Phase 3 studies (double-blind and open-label). The ISS text, however, should describe the entire program, including brief summaries of the safety data from the individual Phase 3 studies. The Phase 1 and Phase 3 studies do not have to be integrated because the two types of study are evaluated independently from one another. Data from the Phase 3 studies go into the label. It is acceptable, however, for the ISS to include the Phase 1 and Phase 3 integration set if the Sponsor elects to perform these analyses.

- B. *The proposed analyses for AEs, laboratory assessments, vital signs, pulse oximetry, and ECGs are included in the ISS SAP. Does the Agency agree that Mallinckrodt's proposed analyses are appropriate (necessary and sufficient) for the integrated analyses? Are*

there additional analyses or evaluations that the Division would like to see addressed in the upcoming NDA?

FDA Response:

Your proposed ISS analysis appears reasonable with the following additions:

- 1. Provide an analysis of liver function laboratory assessments for all pooled and integrated safety datasets**
- 2. Conduct the following SMQ assessments:**
 - a. Severe Cutaneous Adverse Reactions**
 - b. Hepatic Disorders/Drug-Related Investigations**

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion required at this time.

DISCUSSION: No discussion necessary.

Chemistry, Manufacturing, and Controls

DRUG SUBSTANCE

Question 9:

In our EOP1 meeting request (SN 0018, 02 September 2011), Mallinckrodt posed the following question (Question 3): "Mallinckrodt does not plan to conduct any additional nonclinical safety or toxicology studies to support the 505(b)(2) NDA for COV795 unless new signals are evident in the clinical trials or new impurities or degradants require further investigation. Does the Agency agree with this approach?". In the Written Responses of 07 December 2012, the Agency replied to Question 3 as follows:

"Based on preliminary review of your proposed oxycodone drug substance specifications, it appears as though (b) (4) exceed the ICH Q3A(R2) qualification threshold. Your NDA or DMF must contain adequate information to justify these levels. If you intend to justify these levels based on literature, you must include copies of all literature articles referenced."

Section 3.2.S.4.5 of Drug Master File (DMF) # 6930 was revised to include justification for the specification levels for the (b) (4). Referenced literature articles were included in Section 4.3 of the DMF. The justification is provided for the reviewer's convenience in Appendix 2.

Does the Agency agree that the levels of (b) (4) have been appropriately qualified and no further toxicological study is required?

APPEARS THIS WAY ON ORIGINAL

FDA Response:

The drug substance impurities (b) (4)

. Upon preliminary review, the justification provided appears to be acceptable. However, final determination of the adequacy of the data can only be made upon formal review.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comment and will submit the justification in the NDA.

DISCUSSION: No discussion necessary.

Question 10:

Mallinckrodt manufactures both APAP and OC for this drug product. Mallinckrodt will reference its own DMFs (#'s 5326 and 6930) in the dossier. Mallinckrodt will include in the Module 3 drug substance section:

- ***Copies of Certificates of Analysis (CoAs) for 1 lot each of OC and APAP from both*** (b) (4) ***(drug product manufacturing site) and Mallinckrodt***
- ***(b) (4) specification sheets for both APIs***
- ***Letters of authorization to our DMFs.***

A. Does the Agency agree that this approach is complete and fileable?

B. Are there Agency expectations to further describe APAP and oxycodone activities between Mallinckrodt and the contractor drug product site (ie, (b) (4)) in order to make this section more complete for Agency review and approval?

FDA Response:

The approach is reasonable in terms of the fileability of the application and, based on the summary, there are no additional expectations regarding activities between (b) (4) and Mallinckrodt regarding the two drug substances.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Question 11:

Mallinckrodt may add an alternative drug substance supplier or utilize an alternative code of oxycodone HCl after NDA approval. A proposed comparability protocol outline has been included as Appendix 3 for such a proposed supplementary action.

A. Does the agency agree that the outline of expected information is complete? If not, what additional items would be needed?

FDA Response:

The outline of information that is planned for inclusion in the comparability protocol appears reasonably comprehensive. However, final acceptability will be determined at the time of NDA review in conjunction with the review of all pertinent CMC information for both the drug substance and drug product.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments to Questions 11 A and B; no discussion necessary.

DISCUSSION: No discussion necessary.

- B. If issues arise during review of the NDA in regard to the acceptability of the API comparability protocol, can Mallinckrodt withdraw the comparability protocol without impact on the PDUFA timeline?*

FDA Response:

Withdrawal of the protocol during review will not impact the PDUFA timeline.

DISCUSSION: No discussion necessary.

DRUG PRODUCT

Excipients

Question 12

In our EOP1 meeting request (SN 0018, 02 September 2011), Mallinckrodt posed the following question (Question 3): "Mallinckrodt does not plan to conduct any additional nonclinical safety or toxicology studies to support the 505(b)(2) NDA for COV795 unless new signals are evident in the clinical trials or new impurities or degradants require further investigation. Does the Agency agree with this approach?". In the Written Responses of 07 December 2012, the Agency replied to Question 3 as follows:

"(b) (4) is not currently listed in the Inactive Ingredient's Database. As approval of your NDA would result in this excipient being listed in CDER's Inactive Ingredient Database, your NDA must include justification for the maximum daily dose of this potentially novel excipient or the maximum daily dose of the individual components. Reference to information in a DMF must take into consideration the maximum daily dose of the drug product formulation."

In Appendix 4 of the briefing book, Mallinckrodt has provided a table which presents the composition of (b) (4), the corresponding Inactive Ingredient Data (IID) limits and total daily intake (TDI) for each component. As each component complies with the IID limits, Mallinckrodt does not see a need for further evaluation.

Does the Agency agree that (b) (4) would need no further toxicological or technical evaluation?

FDA Response:

The information provided in the FDA Inactive Ingredients Guide is based on a per-dose maximum. Justification of the safety of the excipients must be based on a total daily intake of the excipient calculated for maximum daily dose (MDD) of the active ingredient. The maximum daily dose of your product should be based on the MDD of acetaminophen which is 4 g.

However, we have conducted a preliminary review and it appears that the levels of the individual components of (b) (4), when calculated for the total daily intake of 4 g of acetaminophen, are adequately qualified. Please note that this is a preliminary review and final determination of the adequacy of the data can only be made upon formal review of the NDA.

Include a letter of authorization in the NDA to allow our review of all pertinent CMC information regarding the (b) (4) DMF.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt appreciates the Agency response and guidance to base the MDD of COV795 on the MDD of acetaminophen (4 grams). Using this approach, the MDD of COV795 will be 12 tablets (90 mg of oxycodone HCl and 3900 mg of acetaminophen).

DISCUSSION: No discussion necessary.

Question 13

A list of the excipients, expected TDIs, and IID limits (including Polyox) are included in Appendix 4.

Polyox (polyethylene oxide), sourced from (b) (4), is a component in the formulation at a level of (b) (4) per tablet. According to (b) (4) (see information from (b) (4) in Appendix 5), there have been a series of joint International Pharmaceutical Excipients Council (IPEC), industry and FDA meetings, both past and ongoing, regarding the removal of polyethylene oxide from the FDA's IID.

(b) (4) has claimed (see information from (b) (4) in Appendix 5) that FDA will accept the previous IID maximal allowed amount (i.e., (b) (4) per oral tablet) in conjunction with the appropriate reference to the full toxicity and safety data, per a letter of authorization to DMF # (b) (4) (Section 2.6.6 Nonclinical Toxicology Written Summary of the DMF is provided for convenience in Appendix 6).

A. Does the Agency agree that these expected limits for Polyox are acceptable for NDA filing and approval without further toxicology assessments?

FDA Response:

Please confirm that the Polyox used in your formulation is (b) (4)

Polyox (b) (4) is adequately qualified for safety at the levels in your drug product described in the meeting package for a total daily intake of 4 g of acetaminophen.

Mallinckrodt Pre-Meeting Response:

Polyox (b) (4) has an average molecular weight of approximately (b) (4) (b) (4). This information will be included in the NDA filing. No further discussion necessary.

DISCUSSION: No discussion necessary.

- B. Does the Agency agree that these expected TDI limits and IID levels for the other excipients are acceptable for NDA approval without further toxicology assessments?*

FDA Response:

Justification of the safety of the excipients must be based on the TDI of each excipient calculated for the maximum daily dose (MDD) of the active ingredient. The maximum daily dose of your product should be based on the MDD of acetaminophen, that is, 4 g.

Upon preliminary review, it appears that the levels of the excipients used in your product when calculated for the total daily intake of 4 g of acetaminophen are adequately qualified. Please note that this is a preliminary review and a final determination regarding the adequacy of the data can only be made upon formal review of the NDA.

Mallinckrodt Pre-Meeting Response:

Because of the amounts and ratio of Oxycodone HCl and acetaminophen in the COV795 tablet, a 4 gram daily dose of acetaminophen implies a maximum daily dose of 12 tablets and a MDD of 90 mg of Oxycodone HCl and 3900 mg of acetaminophen. Mallinckrodt would appreciate clarification as to whether it was the Agency's intention that a daily dose of 12 COV795 tablets be used to establish ICH Qualification limits for drug product degradation products that are not metabolites?

DISCUSSION:

The Agency confirmed that the MDD should be based on the MDD of APAP (4000 mg) and that it is therefore appropriate to use 12 COV795 tablets as the MDD when establishing ICH Q3B qualification limits for drug product degradation products that are not metabolites.

Question 14

For commercial purposes, the drug product will be manufactured by (b) (4). Incoming testing and release of the excipients will be performed by (b) (4); however, (b) (4) does not have the capabilities to perform certain attribute tests on some excipients (example Polyox; see Appendix 7 for the analytical standard/specification sheet and specific tests). Therefore, (b) (4) will outsource the testing to certain Good Manufacturing Practices (GMP) analytical laboratories. Mallinckrodt will include the analytical laboratory name, address, contact person at the site with their contact information and registration number in the dossier.

Are there further Agency expectations for supporting documentation (if any) in the dossier for either (b) (4) or the supporting analytical laboratories (e.g., results for testing of Polyox sample(s), further information about the analytical site which will perform the testing, etc)?

FDA Response:

For any excipients tested with non-compendial methods, provide the methods and supporting validation data in the application.

You should have a high degree of confidence that: (1) the contracting partner is currently operating in a state of CGMP compliance and, (2) the testing results from the contracting partner are reliable. Both parties should have a clear understanding, preferably in writing, of expectations, roles and responsibilities. Additionally, all facilities named in a complete submission must be ready for inspection at the time of filing.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Question 15

In lieu of providing each CoA for all excipient lots utilized in the clinical studies and registration batches, Mallinckrodt intends to include a single representative CoA for each excipient in the dossier, as all excipients (with the exception of (b) (4)) are compendial. All CoAs for excipients will be available upon request. Both the supplier and (b) (4) documentation will be provided in the dossier as illustrated in Appendix 8.

A. Does the Agency agree with this approach?

FDA Response:

We agree with the approach proposed.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

B. If not, what is the Agency expectation regarding the inclusion of excipient COAs for key batches (i.e., is the expectation for all pivotal Phase 3 clinical studies, all 3 registration lots; some other lot[s])? In which section would the Division prefer to have these CoAs?

FDA Response: N/A

Question 16

Mallinckrodt understands that, for each component of the drug product (as well as for the drug product itself), [REDACTED] (b) (4)

[REDACTED]

FDA Response:

The proposed use of CoAs in lieu of testing may be adequate, provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals in accordance with 21 CFR 211.84(d)(2).

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Manufacturing Records, Process Development, and Commercial Scale-Up

Question 17

In the submission, Mallinckrodt will describe the approach taken for product development. This approach utilizes a series of systematic processes, starting with an understanding of the patient and care providers' needs, which are then linked with formulation development and process understanding. Included in this development effort was the use of structured experimentation to develop a formulation and process that meet the critical to quality attributes, which link to safety and efficacy. A cause and effect matrix was then utilized to assess the potential impact of materials and process variability. Those material attributes and process parameters with the greatest potential to impact product quality were further

evaluated in a series of designed experiments for each of the unit operations (b) (4)

The target parameters for the designed experiments were based on the pivotal clinical lots and registration lots.



FDA General Comment:

FDA does not approve process validation approaches or protocols. The actual protocols, acceptance criteria, and study outcomes will be evaluated during an inspection. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. The actual protocols, acceptance criteria, and study outcomes will be evaluated during an inspection.

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process.

Please find more information in the guidance for industry, *Process Validation: General Principles and Practices*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

- A. The processing ranges included in the NDA are based on development experiments (b) (4) full commercial scale), theoretical scale-up and modeling principles and previous experience. These ranges may be modified subsequent to scale-up and prior to validation. Does the Agency agree with this approach?*

FDA Response:

The development approach outlined is reasonable. Detailed evaluation will take place at the time of NDA review.

It is expected that increased process understanding gained from scale-up and process validation activities may require changes to processing ranges to improve the process. Any changes should be scientifically justified, adequately controlled and managed within the site's quality system (e.g., change management system).

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the FDA's General Comment and responses to Question 17A, B, C, D, and E. Mallinckrodt intends to scientifically justify the changes in the processing ranges based on data generated during scale-up and process validation; no discussion necessary.

DISCUSSION: No discussion necessary.

- B. Does the Agency have preferred language to identify these ranges (e.g., "planned commercial ranges") versus the process validation ranges, as the process validation ranges may be tighter.*

FDA Response:

The Agency does not have a preferred nomenclature. Your filing should be clear as to the proposed ranges and should be supported with scientific justification (e.g., data, models). Your scale-up and associated process validation protocols should clearly define the processing ranges. Any changes made to the proposed ranges should be documented and scientifically justified.

DISCUSSION: No discussion required.

- C. *In order to demonstrate the performance of the commercial product, during process validation Mallinckrodt will perform [REDACTED] (b) (4) [REDACTED]; and finished product release testing. The process validation lots will be placed on stability according to International Conference on Harmonisation (ICH) conditions. Does the Agency agree that this data will be sufficient to justify the performance of the product?*

FDA Response:

Please see FDA's General Comment regarding Process Validation above.

DISCUSSION: No discussion necessary.

- D. *For the NDA, Section 3.2.P.2 will include a description of the product, which reflects the patient and care providers' needs, along with the identification of the critical to quality attributes. The key material attributes will then be discussed in Section 3.2.P.2.2, while the key processing parameters will be discussed in Section 3.2.P.2.3. Does the Agency agree that these are the appropriate sections within the NDA to discuss the development process?*

FDA Response:

The proposed sections are appropriate for the information cited for inclusion.

Additional Comment:

A complete description of the commercial-scale drug substance and drug product manufacturing processes is required and should include process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) and P.3.3 (drug product) of the application. Notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70. The Agency recognizes that changes to low criticality process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation.

DISCUSSION: No discussion necessary.

- E. *The batch records for pivotal clinical and registration studies are very similar in regard to manufacture (i.e., equipment, size, process parameters, etc). Does the Agency have a*

preference as to which batch records should be included in the dossier if the executed batch records are very similar?

FDA Response:

Submit batch records as per 21 CFR 314.50(d)(1)(ii)(b) for any bioavailability/bioequivalence and primary stability studies.

DISCUSSION: No discussion necessary.

Dissolution testing

Question 18

In response to Question 9 of our EOP1 meeting package (SN 0018, 02 September 2011), the Agency stated that:

“Decreased dissolution at high alcohol concentration may indicate decreased drug solubility at such alcohol concentrations. Therefore, we recommend that lower concentrations (5%, 10%, and 20%) of alcohol also be tested.”

Mallinckrodt has included the results for the requested study in Appendix 9, Section 4.3 of the briefing document.

Does the Agency agree that the results of the completed dissolution testing do not indicate potential for dose-dumping, and that an in vivo human alcohol interaction study will not be necessary to further characterize this formulation?

FDA Response:

Yes, we agree that results of dissolution testing do not indicate potential for dose-dumping in the presence of alcohol, and that an in vivo human alcohol interaction study will not be necessary.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Question 19

In Question 13 of our EOP1 meeting package (SN 0018, 02 September 2011), Mallinckrodt proposed a methodology and general approach for setting dissolution specifications:

Apparatus: USP 2

RPM: (b) (4)

Medium: 900 mL 0.1N HCl

Time points for OC and APAP: 0.50 h, 2 h, 4 h, (b) (4)

Units: Per acceptance table in USP 711 for ER dosage forms

The FDA provided the following response:

1. *Your approach for setting dissolution specifications based on the results from pilot batches produced for bioequivalence testing, clinical testing, and stability is reasonable. However the proposed time points will be a review issue.*
 - *Provide the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time point and specification value) as part of pre-NDA meeting package or NDA submission.*
2. *The use of a paddle speed of (b) (4) rpm is not recommended. The common paddle speeds used with apparatus 2 ranges from 50 to 100 rpm. The proposed dissolution method needs to be supported by the following information:*
 - *Provide dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method as part of pre-NDA meeting package or NDA submission.*
 - *Conduct testing and provide data to demonstrate the discriminating capability of the selected dissolution method.*

The claim of being an extended-release formulation for your proposed product needs to be supported by information that fulfills the 21 CFR 320.25(f) requirements.

In response to the Agency's comment, Mallinckrodt evaluated the product with speeds of (b) (4) 100, (b) (4) RPM. This evaluation led to the choice of 100 RPM as the appropriate paddle speed. In Appendix 9 of the briefing package, Mallinckrodt has included the dissolution profile data (raw data and mean values) from the primary clinical and stability batches which supported our decisions on time points, specification, and paddle speed.

- A. *Does the Agency agree that these data support our decisions on time points and specifications?*

FDA Response:

In general, we agree with your approach of time-point selection and dissolution acceptance criteria. However, the acceptability of the dissolution acceptance criteria will be determined once the totality of the data is reviewed upon NDA submission.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments to Question 19 A, B, and C, and will address Question 19C appropriately in the NDA. No discussion necessary.

DISCUSSION: No discussion required.

B. Does the Agency agree that the earlier time points collected at (b) (4) RPM do not present a review issue, as we have bridged the (b) (4) RPM (older speed) and 100 RPM (current) data? If not, can the Agency elaborate as to how the bridging may be accomplished?

FDA Response:

Yes, we agree that the earlier time points collected at (b) (4) RPM do not present a review issue (see comment below).

DISCUSSION: No discussion necessary.

C. In Section 3.3.4 of Appendix 9, we have included data supporting the discriminating properties of the dissolution method under (b) (4) 100 (b) (4) RPM conditions. Does the Agency agree that the method is acceptable?

FDA Response:

In general, the method seems to appropriately discriminate product batches (b) (4)

DISCUSSION: No discussion necessary.

Question 20:

In reference to the last sentence of the FDA response for Question 13 of our EOP1 meeting package (i.e., "The claim of being an extended-release formulation for your proposed product needs to be supported by information that fulfills the 21 CFR 320.25(f) requirements"), Mallinckrodt believes that the following information will provide justification to support the labeling of COV795 as an ER product. The 21 CFR 320.25(f) requirements are shown below in bold font, followed by the information Mallinckrodt intends to provide in italics. Does the Agency agree that the information outlined below will be sufficient to support a decision on the ER claim?

320.25 Guidelines for the conduct of an in vivo bioavailability study. (f) Extended release formulations.

(1) The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:

(i) The drug product meets the extended release claims made for it.

Clinical study reports from 11 Phase 1 PK, bioavailability, and safety studies will support the extended release claims.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

Clinical study reports from 11 Phase 1 PK, bioavailability, and safety studies, including 3 food-effect studies, will establish the lack of dose dumping for COV795.

(iii) The drug product's steady-state performance is equivalent to a currently marketed nonextended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

Clinical study report from Phase 1 multiple-dose Study 0255 (comparison with LDs Roxicodone and Ultracet; see Section 1.6.2.1.2 of this submission for a brief description of the study; complete study protocols provided in Section 5.3.3.1, SN 0030) will establish there is no difference between the steady-state performance of COV795, Roxicodone and Ultracet with respect to AUC and C_{max} .

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

The consistent PK performance of the current 7.5 mg OC/325 mg APAP formulation will be illustrated by low intra- and inter-subject variability and a lack of outliers for AUC and C_{max} , as demonstrated in Phase 1 multiple-dose cross-over Studies 0172 and 0255 and single-dose cross-over Studies 0170 and 0256.

(2) The reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the extended release claims made for the drug product. The reference material shall be one of the following or any combination thereof:

(ii) A currently marketed noncontrolled release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling of the noncontrolled release drug product.

The reference material, or LD(s) for COV795 are Roxicodone and Ultracet, which are in accordance with 320.25(f)2(ii).

FDA Response:

Yes, the information you have outlined in this submission will be sufficient to support the ER designation claim. However, the acceptability of this claim will be a review issue once all information has been received.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Question 21

The Agency provided the following response to Question 14 of our EOP1 meeting package:

“Also, clarify the nature of debossing for the commercial tablets in the NDA and provide data supporting the comparability of the product performance with and without the debossing.”

In Section 4.2 of Appendix 9 of the briefing document, Mallinckrodt has included a description of the debossing and a photograph of the debossed product. Additionally, comparative hardness and dissolution data is included

Does the Agency agree that this information is adequate, and that no further testing is required for the NDA?

FDA Response:

Yes, hardness information and dissolution profile comparisons in at least three different media are sufficient to support the implementation of debossing. However, given that additional information is needed to support the discriminating ability of the dissolution method, the acceptability of the data will be a review issue.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Packaging

Question 22

Mallinckrodt intends to submit a comparability protocol for changes in the primary container closure. In Appendix 10 of the briefing package, Mallinckrodt has included an outline of the comparability protocol that is planned for submission in the NDA.

A. Based on this outline, does this approach appear adequate and sufficient to support filing and approval of the NDA?

FDA Response:

The outline of information that is planned for inclusion in the comparability protocol appears to be reasonably comprehensive. However, final acceptability will be determined at the time of NDA review in conjunction with the review of all pertinent CMC information for the drug product.

Note that we do not consider matrixing to be appropriate for stability protocols supporting extended-release oral opioid drug products.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments to Question 22 A and B, but seeks further clarification regarding a new closure supplier. Mallinckrodt would appreciate feedback either at the Pre-NDA meeting or in the meeting minutes.

Mallinckrodt is now aware that a new closure (b) (4) supplier will be needed for launch quantities. Although the closure supplier (b) (4) will change, the basic closure composition (b) (4) will remain the same. The product contact surface (b) (4) will remain unchanged. The new closure meets all applicable testing requirements of USP <661> and <671>. All product contact components of the packaging system which afford stability and quality for the product (bottle and

Two possible options exist for the submission of this new closure supplier:
A.) Mallinckrodt will include release data for one lot of product packaged with the new closure in the dossier. Mallinckrodt commits to updating the NDA with full-term stability data for COV795 with this new closure after approval and/or during NDA review, confirming equivalency of the closure systems.
B.) Mallinckrodt would follow the recommendations in the FDA's Guidance for Industry: Changes to an Approved NDA or ANDA (April, 2004) and submit this change in the annual report.

1) Does the Agency agree this proposal is acceptable for filing within the original NDA submission (Option A), or would it prefer to have Mallinckrodt submit per the Guidance (ie, annual report) (Option B)?

2) If the Agency wishes to review the data with the new closure during the review process (Option A), will the Agency accept stability data without extension of the PDUFA date?

DISCUSSION:

The Agency responded that a “hybrid” of the described approaches is preferable. The Sponsor should provide the release data in the NDA submission (“Option A”), and the stability data after approval in the annual report (“Option B”).

B. If issues arise during review of the NDA in regard to the acceptability of the packaging protocol, can Mallinckrodt withdraw the comparability protocol without impact on the PDUFA timeline?

FDA Response:

Withdrawal of the protocol during review will not impact the PDUFA timeline.

DISCUSSION: No discussion necessary.

Question 23

The proposed commercial manufacturing site ((b) (4)) can produce a completed packaging record for any specific manufactured lot, but to due to a GMP internal requirement (see below), it cannot produce a blank proposed commercial packaging record at the time of NDA submission. Mallinckrodt intends to submit a description of the packaging operation (see Appendix 11, Packaging process description), as well as a description of the process for the master packaging record (see below).

As mentioned above, (b) (4) has prerequisites before an official, effective copy of an executable commercial Packaging Work Order can be generated to package product.

These prerequisites include:

- 1) Commercial product name approved by FDA,*
- 2) Material numbers assigned for bulk (i.e., finished tablets) and packaging components,*
- 3) Approved artwork and specifications for packaging components,*
- 4) Approved Bill of Material,*
- 5) Approved Product Specific document,*
- 6) Approved Line Template document,*
- 7) Expiry dating for product approved by FDA, and*
- 8) Bulk yields entered into SAP system.*

For this reason, we cannot provide a "blank" packaging work order for inclusion with the COV795 product NDA submission.

An official, effective copy of a Packaging Work Order consists of three documents that are merged to create one document: 1) Bill of Material - Approved listing of bulk and packaging components (which includes material numbers and descriptions for all items) and quantities of each required to package product (see Appendix 11, Bill of material), 2) Product Specific Document - Approved instructions to package product which are specific to the product and packaging configuration(see Appendix 11, product specific document), and 3) Line Template - Approved document to record in-process checks during the packaging operation (see Appendix 11, Line template). Examples of a Bill of Material, product specific document and

line template and executed batch record (see Appendix 11, Example of Executed Packaging Batch Record) are provided for illustrative purposes. Reconciliation limits for bulk and printed packaging components (for components that reference the product name) reside in the Bill of Material for each item. Reconciliation limits for reconcilable materials are printed in the official, effective copy of the Packaging Work Order that is used to package product. Any changes in the Bill of Material (which control the limits) are done through the change control system.

Does this outline and approach appear adequate and sufficient to support filing and approval of the NDA?

FDA Response:

In lieu of a proposed master commercial packaging record, the information in your filing regarding packaging operations must sufficiently describe the packaging activities of your manufacturer. The actual procedures and documentation used to support commercial operations will be evaluated during an on-site inspection. Your manufacturer must be in compliance with all applicable regulations found in 21 CFR 210 and 211, including those of 21 CFR 211 subpart G and subpart J.

Mallinckrodt Pre-Meeting Response:

Mallinckrodt acknowledges the Agency comments; no discussion necessary.

DISCUSSION: No discussion necessary.

Microbial Testing

Question 24

Mallinckrodt evaluated all 3 registration batches for total aerobic microbial count, total yeasts and molds count, and for the specified organism E. coli as recommended for "Non-aqueous preparations for oral use" by USP <1111> Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use. (b) (4)

Results are provided in Appendix 12 of the briefing document.

Does the Agency agree that the data collected demonstrates that microbial limit testing is not needed on the commercial product?

FDA Response:

The decision to allow no testing for microbial limits at release will be made as part of the NDA review. The data and reasoning to support this decision should be provided in the Pharmaceutical Development section of the application and could contain the following items: (b) (4)

microbial limits test results for multiple batches of the product at release and during the stability program; any available microbial limits data from the drug substance and other components of the drug product.

***Mallinckrodt Pre-Meeting Response:
Mallinckrodt acknowledges the Agency comments; no discussion necessary.***

DISCUSSION: No discussion necessary.

Environmental Assessment

Question 25

Mallinckrodt believes that COV795 qualifies for a categorical exclusion based upon 25.31(a), as action on the NDA will not “increase the use of the active moiety” (note that 25.5(b)(4) defines that increased use may occur if the drug will be administered at higher dosage levels, for longer duration or for different indications than were previously in effect). COV795 is not seeking approval of higher dosage levels, longer duration, or different indications than that previously approved for the active moieties (OC and APAP).

Does the Agency agree that Categorical Exclusion from the Environmental Assessment under 25.31(a) is acceptable for COV795 and will be granted during the NDA review?

FDA Response:

After discussion with the environmental assessment (EA) staff, it has been determined that the EA Guidance document provides the following definition for ‘no increased use’ that appears to pertain to this application: Combination drugs in which the single product substitutes directly for two approved products that would be administered separately. In such cases, an exclusion under 21 CFR 25.31(a) is appropriate for the NDA in terms of the environmental assessment.

***Mallinckrodt Pre-Meeting Response:
Mallinckrodt appreciates the Agency guidance; no discussion necessary.***

DISCUSSION: No discussion necessary.

Additional Clinical Pharmacology Comment:

Address dose adjustment in special populations and Drug-Drug Interaction potentials in the NDA submission. You may obtain the information from the listed drug’s label and/or literature.

***Mallinckrodt Pre-Meeting Response:
Mallinckrodt appreciates the Agency guidance; no discussion necessary.***

Additional Comment from the Division of Medication Error Prevention and Analysis:

Although your product is still in the investigational stage, we suggest differentiation of your product from the currently marketed immediate-release oxycodone/acetaminophen products once submitted for formal review:

- a. If a proprietary name is to be submitted for this product, consider a distinct proprietary name to include a modifier since its proposed frequency of administration is every 12 hours. Preliminary search of drug usage data indicates that immediate-release oxycodone/acetaminophen products may also be prescribed every 12 hours. Additionally, the medical community is accustomed to cutting, crushing, splitting, and/or chewing oxycodone/acetaminophen immediate-release products, and recent postmarketing cases have reported wrong technique errors (e.g., cutting, crushing, splitting, and/or chewing) of extended-release drug products that do not contain a modifier in the proprietary name. Therefore, since there are both overlapping product strengths and frequency of administration between your proposed product and the immediate-release oxycodone/acetaminophen products, the extended-release properties of this product may easily be overlooked and should be conveyed in the proprietary name, if you choose to submit one for review.**
- b. Please note that an overlap in strength between the currently marketed immediate-release oxycodone/acetaminophen and the proposed product will require educational, label and labeling strategies to avert potential confusion between the oxycodone/acetaminophen immediate-release products and this extended-release formulation.**

Mallinckrodt Pre-Meeting Response:

Mallinckrodt is planning a proprietary name request for the first quarter of 2012 and will address the Agency comments in that submission.

KEY DISCUSSION POINTS:

1.  (b) (4)
2. The pediatric program will be submitted with the NDA.
3. Abuse-related data will be presented in Module 5 with a link from the Module 1 summary. The Module 1 summary will link to a table in Module 5 and adverse event data in the ISS.
4. This product is considered a class member of the ER/LA opioids and thus must be incorporated into the ER/LA opioid class REMS. Information unique to this product will be presented in the Medication Guide and the Educational Blueprint. The Medication Guide must mirror the label and conform to the one-page format.

5. The final SAP for this product did not include “subject” so this term is not of concern. The Sponsor will submit the analysis as described in the SAP. Any additional post-hoc analysis will be reviewed as well but will be considered post-hoc.
6. Rescue medication data to establish dosing interval should include median time to rescue and amount of rescue.
7. For the ISS, the Sponsor will integrate the Phase 3 data as described in the ISS SAP. The ISS should contain tables that link back to the individual Phase 3 study reports. The ISS text should describe the entire program. Pooling of Phase 1 and Phase 3 studies is not necessary.
8. The MDD should be based on the MDD of APAP (4000 mg). Therefore it is appropriate to use 12 COV795 tablets as the MDD when establishing ICH Q3B qualification limits for drug product degradation products that are not major metabolites.
9. A hybrid approach should be used when supporting the change in the container closure system. Release data should be submitted with the NDA and stability data may be submitted after approval, in an annual report.
10. It is unlikely that an Advisory Committee will be convened for this product but that decision will be made upon submission of the NDA. If the Sponsor requests a priority review, a decision as to whether an Advisory Committee meeting will be needed will likely be made within 30 days of NDA submission.
11. The NDA is planned for submission during the second quarter of 2013.

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

/s/

LISA E BASHAM
01/07/2013



IND 104702

**MEETING REQUEST -
Written Responses**

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Kevin Healy, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Healy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for COV795.

We also refer to your amendments dated September 2 and October 10, 2011, and to our July 20, 2011, communication notifying you that we would provide a written response to the questions in your July 12, 2011, meeting request within 90 days after receiving your background materials. The background materials were received on September 2 and October 10, 2011.

Our responses to your questions are enclosed. If you have additional questions, you must submit a new meeting request.

Question 1:

COV795 is a multilayer ER oral formulation of OC and APAP. An NDA for COV795 is anticipated to be submitted under 21 CFR 314.50 Section 505(b)(2). (b) (4)

[Redacted]

[Redacted] (b) (4)

B)

(b) (4)

C)

(b) (4) fully support a 505(b)(2) application for COV795, then Mallinckrodt is willing to complete PK studies and cite two additional products for the LDs (Roxicodone NDA 021011 and Ultracet NDA 021123). Does the Agency agree that Roxicodone NDA 021011 is an appropriate LD to support the OC component of COV795, and Ultracet NDA 021123 is an appropriate LD to support the APAP component of COV795?

FDA Response: Your proposal to rely upon the Agency's prior findings of safety and efficacy for Roxicodone NDA and the Ultracet NDA is acceptable.

i.

(b) (4)
Mallinckrodt believes that it is important to continue to include Percocet as a (b) (4) comparator in the planned/conducted clinical studies, as Percocet establishes the scientific bridge between the individual APIs and the therapeutic combination. Does the Agency agree that Percocet could be included as a LD to support the individual API component (eg, Roxicodone and Ultracet) LDs?

FDA Response: Percocet should not be listed as a referenced drug. However, we agree that a relative bioavailability study to Percocet would provide the important support for the proposed combination of 7.5 mg of oxycodone and 325 mg of acetaminophen.

ii.

(b) (4)

iii.

(b) (4) fully support the 505(b)(2) application for COV795, Mallinckrodt intends to establish the PK comparability between COV795 and the new LDs (eg, Roxicodone and Ultracet) by studying each of the new LDs in a single and multiple-dose PK study. Mallinckrodt intends

to dose-normalize for any differences in total daily doses of OC or APAP. Does the Agency agree that the Sponsor's revised clinical development plan (addition of these single and multiple dose PK studies) can be sufficient to support the 505(b)(2) application? Can the Agency provide any further guidance on analysis of the PK parameters that will be necessary to establish PK comparability to support the 505(b)(2) application?

FDA Response: Your proposal of conducting single- and multiple-dose PK studies using Roxicodone and Ultracet as LDs is acceptable to support the NDA filing. Whether the information will support the approval of the NDA will be determined after review of the data. The Agency understands that the plasma profiles between ER and IR formulations will be different from the proposed relative bioavailability studies. Although the proposed studies are not bioequivalence studies, the Agency recommend that you still perform a bioequivalence analysis when PK parameters, e.g., Cmax, AUC0-t, AUC0-inf, etc., are compared.

- iv. As explained in Question 3 of the End-of-Phase 1 / Pre-Phase 3 Meeting Package (SN 0018, 02 September 2011), Mallinckrodt does not plan to conduct any additional nonclinical safety studies to support the planned 505(b)(2) application. Further, we do not believe that a potential change in the LD(s) should influence the nonclinical safety or toxicology studies required to support approval of this OC/APAP combination product. Does the Agency agree with this approach?

FDA Response: Yes, the Agency agrees that no new nonclinical pharmacology or toxicology studies are needed for oxycodone or acetaminophen drug substances to support a 505(b)(2) NDA for COV795. However, we note that your application must include adequate drug product labeling that includes nonclinical reproductive and developmental toxicity, carcinogenesis, mutagenesis, and impairment of fertility sections of the label. As you will be relying upon data that you do not own or have right of reference to as the basis of your NDA, your listed drugs relied upon for approval should be selected in order to adequately address these aspects of your label where possible. Your proposed drug product labeling may also be based on information in the literature, if deemed adequate and available. Copies of all referenced citations should be included in the NDA. Reference to an approved NDA label or reference to published articles that refer to a specific branded product will require adequate patent certification. See the response to question 3 for further nonclinical recommendations regarding your application.

- D) Mallinckrodt understands that the DAAAP (b)(4) involved in determining the appropriateness of the LD for 505(b)(2) NDAs, and Mallinckrodt reserves the right to revisit the LD determination. Most important to Mallinckrodt is confirmation (b)(4) that the LD advice given for this submission is consistent with current Agency thinking.

(b)(4)

(b) (4)

FDA Response: A 505(b)(2) application is one that contains “full reports of investigations” of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference of use. Therefore, the listed drug relied upon for approval must be an application approved under section 505(c) of the Act. Applications approved under section 505(j) do not contain full reports of investigations of safety or effectiveness and, therefore, may not be relied upon for approval of an application submitted pursuant to section 505(b)(2). (b) (4)

Question 2:

Mallinckrodt intends to establish the safety and efficacy of COV795 in adult patients prior to conducting pediatric studies. However, to facilitate planning of pediatric studies that may be required under the Pediatric Research Equity Act (PREA) or be necessary to fulfill a Written Request (WR) issued under the Best Pharmaceuticals for Children’s Act, Mallinckrodt appreciates feedback from the Agency regarding the type of studies that may be required. Given that oxycodone and APAP have been used and studied extensively in the pediatric population, Mallinckrodt envisions testing COV795 in a population that can swallow the ER tablet and is therapeutically appropriate (b) (4)

1. Does the Division agree with the Sponsor’s approach of deferring pediatric studies until the safety and efficacy of COV795 has been established in adults?

FDA Response: In general, pediatric studies may be deferred until the safety and efficacy of a new product are established in adults. However, as a reformulation of drug substances that have known safety profiles, oxycodone and acetaminophen, there is no apparent reason to delay initiating pediatric studies once an appropriate formulation is available. A pediatric plan must be submitted with the NDA that includes requests and justifications for waivers and deferrals, the proposed study plan, and a time line including the dates of the final protocol submission to the Agency, the study completion, and the submission of the study reports to the Agency.

2. Does the Agency agree that studies conducted in a population that can swallow the ER tablet would be sufficient for satisfying a potential WR? Please provide additional guidance.

FDA Response: Under PREA, you are required to conduct studies in the entire pediatric age range if the indication is applicable to pediatric patients. Since the proposed indication of acute pain is applicable to the entire pediatric population, you must attempt to develop an age-appropriate formulation of this product to

assess PK and safety in all age groups, in addition to efficacy in pediatric patients less than 2 years of age. Therefore, it is not appropriate to limit the population based on the ability to swallow an ER tablet.

Written Requests are issued as described in the Best Pharmaceuticals for Children Act (BPCA), and are not mandatory. However, a Written Request (WR) is based on the active moieties in the drug product, and all indications including possible off-label indications may be included in the required studies for a WR. It is also not appropriate to limit the pediatric population included in a WR for your product to patients who can swallow an ER tablet.

Question 3:

Mallinckrodt does not plan to conduct any additional nonclinical safety or toxicology studies to support the 505(b)(2) NDA for COV795 unless new signals are evident in the clinical trials or new impurities or degradants require further investigation. Does the Agency agree with this approach?

FDA Response: No new nonclinical pharmacology or toxicology studies are needed for oxycodone or acetaminophen drug substances to support a 505(b)(2) NDA for COV795.

Based on preliminary review of your proposed oxycodone drug substance specifications, it appears as though (b)(4) exceed the ICH Q3A(R2) qualification threshold. Your NDA or DMF must contain adequate information to justify these levels. If you intend to justify these levels based on literature, you must include copies of all literature articles referenced.

(b)(4) is not currently listed in the Inactive Ingredient's Database. As approval of your NDA would result in this excipient being listed in CDER's Inactive Ingredient Database, your NDA must include justification for the maximum daily dose of this potentially novel excipient or the maximum daily dose of the individual components. Reference to information in a DMF must take into consideration the maximum daily dose of the drug product formulation.

Question 4:

Does the Agency agree that the COV795 Phase 1 program will establish the comparability of exposure between COV795 and the LD, (b)(4) and concur that this Phase 1 PK program is sufficient to support the filing and eventual approval of the NDA?

FDA Response: The types of information obtained from three Phase 1 studies are not sufficient to support the filing. As a novel, extended-release formulation relying upon the Agency's prior findings of safety and efficacy for immediate-release products, you must demonstrate that the new PK profile for your product is capable of providing efficacy. The approval of the NDA will be a review issue.

Question 5:

Mallinckrodt concludes that Studies 0171, 042, and 044 have sufficiently characterized a minimal food effect with COV795, and thus no further characterization is planned for our upcoming studies.

- A. Does the Division agree that the Sponsor's Phase 1 studies have established that, at the intended COV795 dose administration (7.5 mg OC/325 mg APAP, 2 tablets Q12h), there is not a meaningful food effect?

FDA Response: Yes.

- B. Does the Division agree that no further characterization of a potential food effect is necessary for the COV795 development program?

FDA Response: Yes.

- C. Does the Division agree that, upon successful completion of the COV795 clinical development program, labeling for COV795 should state that COV795 can be administered without regard to food?

FDA Response: Yes.

Question 6:

Mallinckrodt would appreciate Agency feedback on protocol COV15000182, and has specific questions on the following aspects of the protocol:

- A. Within the double-blind phase of Protocol COV15000182, there is a single-dose period designed to evaluate the onset and duration of COV795 analgesia, followed by a multiple-dose regimen (doses 2, 3, 4, and 5). Does the agency have any concerns with this design?

FDA Response: The evaluation plan for the onset and duration of analgesia after the first dose (single-dose period) is not acceptable. Do not withdraw subjects who use rescue medication less than an hour following the first dose. These subjects must be included in the analyses of SPID 48, onset, and duration of action. You also propose to administer a second dose as soon as one hour following the first dose in subjects requesting additional treatment. This may be acceptable if you plan to label the product to include a loading dose, i.e., a repeat dose in one hour, followed by every 12 hour dosing. If the interval between the first and second dose is not fixed, then you will need to develop and justify a formula for computing the SPID48 that includes subjects who only receive the first dose. You must also propose a method of calculating the onset of action in subjects taking an early second dose of COV795.

You are proposing to develop COV795 for the management of acute pain. We are concerned that the onset of action for this extended-release product will not be appropriate for an acute indication. You must demonstrate that COV795 has an

onset of action, i.e., meaningful onset of pain relief based on the double-stopwatch method, that is reasonable for the treatment of acute pain. In general, drugs approved for acute pain have an onset of action within one hour.

- **You may consider assessing the single-dose effects of COV795 in a dedicated single-dose study, and the multiple-dose effects in a second study. However, the decision is yours.**

- B. Does the agency agree with the primary endpoint being SPID₄₈, including the timing of these 48 hours to start at the 2nd dosing?

FDA Response: The SPID48 is an acceptable primary endpoint for an acute pain indication. However, the timing for evaluation of SPID48 must start from time zero after the first dose. See response to Q6A above.

- C. Does the agency agree with using the multiple imputation methodology as proposed in the protocol?

FDA Response: The proposed methodology assumes that the data are missing at random (MAR). A missing not at random (MNAR) mechanism is appropriate for analgesic trials since a subject who discontinues early is likely to be experiencing a poor clinical outcome. Moreover, it is not appropriate to treat the data from subjects who have taken rescue as MAR. The National Academy of Sciences (NAS) released a report on missing data which was commissioned by FDA. We recommend that you consult this report and propose a suitable MNAR method. We will review your proposal as resources allow. The report can be found at: http://books.nap.edu/openbook.php?record_id=12955.

- D. Does the agency agree that the suggested sensitivity analyses for the primary analysis are adequate and sufficient to demonstrate efficacy of COV795?

FDA Response:

- **The first analysis, which uses single-imputation methods for patients who drop out due to an adverse event or lack of efficacy, may be informative.**
- **The second analysis, which statistically adjusts for use of rescue medication, would be less useful. The rescue-adjusted treatment effect would be difficult to interpret.**
- **You should consult the NAS report for additional ideas for sensitivity analyses.**

Additional comments on the Phase 3 acute pain trial:

- **Your proposed primary analysis model includes a term for the treatment-by-center interaction. In your statistical analysis plan, you must pre-specify how the treatment effect will be estimated (e.g., Type II sum of squares).**

- **On page 8 of the Statistical Analysis Plan, you state, “If rescue medication is required/requested less than 1 hour prior to 1st dose of study medication, the subject will be dropped from the study. These dropped subjects will be replaced by a subject randomized to the identical treatment group.” Considering that the study will be blinded, clarify how you will assign a different subject to the same group.**
- **If you plan to label COV795 to be administered as 1 to 2 tablets every 12 hours, you must also establish the efficacy of 1 tablet in your Phase 3 program.**

Question 7:

Mallinckrodt would appreciate Agency feedback on protocol COV15000181, and has specific questions on the following aspects of the protocol:

- A. Does the Division agree that the patient population (osteoarthritis and low back pain patients) selected for this study is appropriate?

FDA Response: The study populations, OA and CLBP patients, for the proposed open-label safety study appears acceptable to obtain safety data. However you may not obtain claims regarding the use of COV795 for chronic pain based on this study.

- B. Does the Division agree that the lead-in titration approach planned for Days 1-7 of this study, used for those patients who do not initially tolerate 2 tablets of COV795, supports an intended dosing regimen of 2 tablets Q12h?

FDA Response: No, it is not appropriate for a drug intended to treat acute pain to require a titration period. The expectation for this indication is that the pain is relieved within the first dosing period.

- C. Does the Division agree that, when combined with the safety database from other COV795 studies, the number of subjects planned for this study (up to 400 subjects to yield at minimum 250 subjects treated with 2 tablets of COV795 Q12h for at least 10 days) is sufficient for establishing the safety profile and supporting the registration of COV795?

FDA Response: Yes, the proposed safety database appears sufficient to support filing the application for an acute pain indication as long as no safety signals arise that requires additional study.

Question 8:

Assuming Mallinckrodt provides evidence of clinically significant efficacy and acceptable safety in the Phase 3 program, does the Agency agree that the Phase 3 program (designed as a single adequate and well controlled study and an open-label safety study) is adequate to support the safety and efficacy for the proposed indication (management of (b) (4) acute pain where the use of an opioid analgesic is appropriate)?

FDA Response: Yes, the proposed Phase 3 program (one efficacy trial and one open-label safety trial) appears acceptable to support filing an application for an acute pain indication.

Question 9:

... Furthermore, the product labeling for COV795 will contain similar warnings regarding the use of alcohol as those described on the package insert for (b) (4) Percocet. Therefore, a biowaiver is requested for an *in vivo* alcohol interaction PK study. Does the Agency agree with this approach?

FDA Response: Decreased dissolution at high alcohol concentration may indicate decreased drug solubility at such alcohol concentrations. Therefore, we recommend that lower concentrations (5%, 10%, and 20%) of alcohol also be tested.

Question 10:

Mallinckrodt intends to conduct a variety of studies to assess the abuse potential of COV795. A series of *in vitro* extractability studies will be performed on the final dosage form. A human abuse liability study is under consideration; this study would be conducted in (b) (4) subjects. Mallinckrodt would appreciate Agency feedback on Mallinckrodt's planned abuse assessment studies, and specifically would appreciate feedback on the following questions.

- A. Given that Mallinckrodt intends to request a Schedule II designation for COV795, is the human abuse liability study a required assessment?

FDA Response: No

1. **A human abuse liability study is not required for the purposes of establishing the proper scheduling of COV7956, with the understanding that this product would be in Schedule II. However, a human abuse liability study may be required to characterize the abuse-deterrent properties of the formulation. Such a study would be particularly warranted if *in vitro* manipulation and chemical extraction studies indicate that the controlled-release properties of COV795 can be compromised facilitating oral, intranasal, or intravenous abuse.**

In the absence of protocols, we cannot comment on the "planned abuse assessment studies." When considering specific studies to evaluate the abuse potential of the to-be-marketed formulation of COV795, you are encouraged to consult:

- a) **FDA presentation entitled "Premarketing Assessment of Abuse-Deterrent Formulations" given before the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting held on October 21, 2010, in Gaithersburg, Maryland**
(<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMa>)

terials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM236243.pdf); and

- b) January 2010 Draft Guidance for Industry *Assessment of Abuse Potential of Drugs* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

B. In designing a potential human abuse liability protocol, Mallinckrodt intends to follow the direction provided in the January 2010 draft Guidance for Industry, "Assessment of Abuse Potential of Drugs." Would the Agency be willing to review and comment on a protocol prior to initiation of this study?

FDA Response: Yes. We are willing to provide comments on a complete protocol for a human abuse potential study of the to-be-marketed COV795 product.

C. Because of the low dose of OC in the current COV795 formulation (7.5 mg) (b) (4) % of this dose (b) (4)

Mallinckrodt believes that the abuse liability of COV795 is relatively low, and that a REMS program likely will not be needed. Does the agency concur with this approach?

FDA Response: No. If you intend to make any claim that COV795 has a lower abuse liability than other extended-release opioids, you will need to conduct adequately designed studies preapproval that support your claim.

Question 11:

COV795 (7.5 mg OC/325 mg APAP) is designed to be dosed as 2 tablets Q12h, thus the maximum daily dose (MDD), per the labeled dose of OC will be 30 mg and the maximum total daily dose of APAP will be 1,300 mg. The MDD of COV795 is lower than the MDD of previously approved strengths of IR OC/APAP combination products. Per International Conference on Harmonization (ICH) Q3B(R2) Impurities in New Drug Products, the following thresholds for Reporting, Identification, and Qualification will be set based on the MDD for each specific active ingredient in COV795, OC and APAP.

ICH Thresholds	Oxycodone Hydrochloride	Acetaminophen
Reporting	(b) (4)	(b) (4)
Identification		
Qualification		

Does the Agency concur with this approach to applying ICH criteria to this fixed dose combination drug product based on the maximum daily dose specified in the labeling?

FDA Response: In general we agree with your approach to applying the reporting, identification, and qualification thresholds of ICH Q3B(R2), recognizing that lower thresholds may be needed if degradants are unusually toxic or contain structural alerts for genotoxicity (e.g., (b)(4)).

Question 12:

Does the Agency agree that the limit of (b)(4) % for (b)(4) is an appropriate drug product degradation specification for COV795 tablets?

FDA Response: From a nonclinical pharmacology/toxicology perspective, the adequacy of your proposed drug product specification for (b)(4) will be determined upon review of the data submitted in the DMF during NDA review. We note that the current electronic submissions to the DMF do not appear to contain any toxicology data. If possible, we encourage you to submit electronic copies of these data to the DMF in Module 4.

Question 13:

Does the Agency agree with the methodology below and general approach for setting the dissolution specifications?

Apparatus: USP 2

RPM: (b)(4)

Medium: 900 mL 0.1N HCl

Time points for OC and APAP: 0.50 hr, 2 hr, 4 hr, (b)(4)

Units: Per acceptance table in USP 711 for ER dosage forms

FDA Response:

- 1. Your approach for setting dissolution specifications based on the results from pilot batches produced for bioequivalence testing, clinical testing, and stability is reasonable. However the proposed time points will be a review issue.**
 - Provide the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time point and specification value) as part of pre-NDA meeting package or NDA submission.**
- 2. The use of a paddle speed of (b)(4) rpm is not recommended. The common paddle speeds used with apparatus 2 ranges from 50 to 100 rpm. The proposed dissolution method needs to be supported by the following information:**
 - Provide dissolution method report including the complete dissolution profile data (individual, mean, SD, profiles) collected during the development and validation of the proposed dissolution method as part of pre-NDA meeting package or NDA submission.**
 - Conduct testing and provide data to demonstrate the discriminating capability of the selected dissolution method.**

- 3. The claim of being an extended-release formulation for your proposed product needs to be supported by information that fulfills the 21 CFR 320.25(f) requirements.**

Question 14:

Does the Agency agree that the available stability data will be sufficient for NDA filing? If the proposed amount of data is not sufficient, does the Agency agree that submission of additional time points during the review cycle without extension of the PDUFA goal date is acceptable?

Does the Agency agree that 24 months of tentative expiration dating may be granted based on acceptable room temperature and accelerated stability data following the stability matrix presented in Table 2?

FDA Response: The available stability data planned to be provided will be sufficient for NDA filing. Submit the maximum available stability data at the time of NDA submission. Amendments to the NDA during the review cycle may not be reviewed based on available resources and compliance to GRMP guidelines. Also, clarify the nature of debossing for the commercial tablets in the NDA and provide data supporting the comparability of the product performance with and without the debossing.

Question 15:

Are the drug substance specifications for Oxycodone Hydrochloride (OC) and Acetaminophen (APAP) adequate to support filing and potential approval of the NDA? Please see Letter of Authorizations provided in Section 1.4.1 (SN 0006, 08 November 2010) for complete access to DMF 6930 (OC) and DMF 5326 (APAP).

FDA Response: The drug substance specifications are adequate to support the filing of the NDA. A detailed evaluation of the specifications to support the approval of your NDA will be performed after the application has been filed.

Question 16:

Mallinckrodt intends to establish drug product specifications in accord with ICH Q6A for COV795. The following quality attributes provided in Table 3 will be monitored during in-process, release and stability testing. Appropriate acceptance criteria will be established using the data accumulated during development, as summarized below.

Does the Agency agree the proposed tests will be sufficient to support filing and potential approval of the NDA?

Response: The tests proposed are sufficient to support the filing of the NDA. The absence of microbial limit testing of the drug product will need scientific justification and may be consulted to the Microbiology team during NDA review.

If you have any questions, contact Allison Meyer, Senior Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ALLISON MEYER
12/07/2011