CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
208090Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 208090  SUPPL #  HFD # 170

Trade Name:  Xtampza ER

Generic Name   oxycodone extended-release capsules

Applicant Name   Collegium Pharmaceutical, Inc.

Approval Date, If Known    April 26, 2016

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)

   b) 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.

   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
c) Did the applicant request exclusivity? 

YES ☐ NO ☒

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

d) 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?

No

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.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
For additional oxycodone containing products, refer to the Orange Book.

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#
NDA#
NDA#

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:

(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:

(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?
If yes, explain:

(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:

Investigation #1

Study CP-OXYDET-08, A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Efficacy Study of Oxycodone DETERx™ Versus Placebo in Opioid-Experienced and Opioid-Naive Subjects with Moderate-to-Severe Chronic Low Back Pain

Study CP-OXYDET-21, Assessment of the Relative Human Abuse Potential of Intranasal Oxycodone DETERx®

Study CP-OXYDET-24, Assessment of the Oral Human Abuse Potential of Oxycodone DETERx

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

Investigation #2

Investigation #3

Reference ID: 3918971
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 ✗ |
| Investigation #3 | YES | NO ✗ |

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

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 CP-OXYDET-08**, A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Efficacy Study of Oxycodone DETERx™ Versus Placebo in Opioid-Experienced and Opioid-Naive Subjects with Moderate-to-Severe Chronic Low Back Pain

- **Study CP-OXYDET-21**, Assessment of the Relative Human Abuse Potential of Intranasal Oxycodone DETERx®

- **Study CP-OXYDET-24**, Assessment of the Oral Human Abuse Potential of Oxycodone DETERx

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 # 75786

YES ☒ NO ☐

Explain:

Investigation #2

IND # 75786

YES ☒ NO ☐

Explain:

Investigation #3

IND # 75786

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?

Investigation #1

YES ☐ NO ☐

Explain:

Investigation #2


(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:

=================================================================
Name of person completing form: Ayanna Augustus
Title: Sr. Regulatory Health Project Manager
Date: March 29, 2016

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Director, DAAAP

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/

AYANNA S AUGUSTUS
04/26/2016

SHARON H HERTZ
04/26/2016
## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>NDA Supplement #</th>
<th>BLA #</th>
<th>BLA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>208090</td>
<td></td>
<td></td>
<td></td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
</tr>
</tbody>
</table>

**Proprietary Name:** Xtampza  
**Established/Proper Name:** oxycodone extended-release  
**Dosage Form:** capsule  
**RPM:** Ayanna Augustus  
**Applicant:** Collegium Pharmaceutical, Inc  
**Agent for Applicant (if applicable):**  
**Division:** Anesthesia, Analgesia and Addiction Products

### For ALL 505(b)(2) applications, two months prior to EVERY action:

- 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)
  - No changes
  - New patent/exclusivity (notify CDER OND IO)

**Date of check:** April 21, 2016

**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.

### Actions

- **Proposed action**
- **User Fee Goal Date is April 26, 2016**

**Previous actions (specify type and date for each action taken)**

- **None**  
- **Tentative Approval, November 6, 2015**

### Application Characteristics

**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.

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, 505(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 Reference ID: 3922927
Review priority:  ☒ Standard  ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track   ☐ Rx-to-OTC full switch
☐ Rolling Review  ☐ Rx-to-OTC partial switch
☐ Orphan drug designation  ☐ Direct-to-OTC
☐ Breakthrough Therapy designation

(NOTE: Set the submission property in DARTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

<table>
<thead>
<tr>
<th>NDAs: Subpart H</th>
<th>BLAs: Subpart E</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Accelerated approval (21 CFR 314.510)</td>
<td>☐ Accelerated approval (21 CFR 601.41)</td>
</tr>
<tr>
<td>☐ Restricted distribution (21 CFR 314.520)</td>
<td>☐ Restricted distribution (21 CFR 601.42)</td>
</tr>
<tr>
<td>☐ Approval based on animal studies</td>
<td>☐ Approval based on animal studies</td>
</tr>
</tbody>
</table>

☐ Submitted in response to a PMR  ☐ MedGuide
☐ Submitted in response to a PMC  ☐ Communication Plan
☐ Submitted in response to a Pediatric Written Request  ☐ ETASU

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

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  - ☐ Yes  ☐ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    - ☐ Yes  ☐ No
  
    - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    - ☐ No  ☐ 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.
    - ☐ Verified  ☐ 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 (approvals only)
  - ☐ Included

Documentation of consent/non-consent by officers/employees
  - ☐ Included
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - Approval: XX, 2016; Tentative Approval: November 6, 2015

### Labeling

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included

- **Medication Guide/ Patient Package Insert/ Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
  - Original applicant-proposed labeling
    - Included

- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most recent draft labeling
    - Included

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - February 2, 2015
  - January 28, 2015

- **Labeling reviews** *(indicate dates of reviews)*

### Administrative / Regulatory Documents

- **RPM Filing Review**/*Memo of Filing Meeting** *(indicate date of each review)*
  - February 11, 2015
  - Not a (b)(2)

- **All NDA 505(b)(2) Actions**
  - Date each action cleared by 505(b)(2) Clearance Committee

- **NDAs only: Exclusivity Summary** *(signed by Division Director)*
  - Included

- **Application Integrity Policy (AIP) Status and Related Documents**
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - Yes
    - No

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- This application is on the AIP
  - If yes, Center Director’s Exception for Review memo (indicate date)
  - If yes, OC clearance for approval (indicate date of clearance communication)
  - ☐ Yes  ☒ No

- Pediatrics (approvals only)
  - Date reviewed by PeRC  September 30, 2015
  - If PeRC review not necessary, explain: *

- Breakthrough Therapy Designation
  - ☒ N/A

- Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)

- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)

- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)

  (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)


- Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include previous action letters, as these are located elsewhere in package)

- 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)

- Minutes of Meetings
  - If not the first review cycle, any end-of-review meeting (indicate date of mtg)
    - ☒ N/A or no mtg
  - Pre-NDA/BLA meeting (indicate date of mtg)
    - ☐ No mtg  April 16, 2014
  - EOP2 meeting (indicate date of mtg)
    - ☐ No mtg  March 30, 2010
  - Mid-cycle Communication (indicate date of mtg)
    - ☒ N/A
  - Late-cycle Meeting (indicate date of mtg)
    - ☒ N/A
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)
    - N/A
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<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tr>
<td>Advisory Committee Meeting(s)</td>
<td>☐ No AC meeting</td>
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<tr>
<td>Date(s) of Meeting(s)</td>
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<tr>
<td>Division Director Summary Review</td>
<td>☐ None November 6, 2015, April 26, 2016</td>
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<tr>
<td>Cross-Discipline Team Leader Review</td>
<td>☐ None</td>
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<tr>
<td>PMR/PMC Development Templates</td>
<td>☐ None</td>
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<tr>
<td>Decisional and Summary Memos</td>
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<tr>
<td>Office Director Decisional Memo (indicate date for each review)</td>
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<tr>
<td>Division Director Summary Review (indicate date for each review)</td>
<td>☐ None November 6, 2015, April 26, 2016</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader Review (indicate date for each review)</td>
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<tr>
<td>PMR/PMC Development Templates (indicate total number)</td>
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<tr>
<td>Clinical</td>
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<tr>
<td>Clinical Reviews</td>
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<td>Clinical review(s) (indicate date for each review)</td>
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<td>Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
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<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR</td>
<td>See clinical review</td>
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<tr>
<td>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)</td>
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<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>☒ None</td>
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<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>☒ N/A September 9, 2015</td>
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<td>Risk Management</td>
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<td>REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))</td>
<td>☐ None April 21, 2016, October 13, 2015</td>
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<td>REMS Memo(s) and letter(s) (indicate date(s))</td>
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<td>Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td>☒ None October 13th and 30th, 2015</td>
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<tr>
<td>OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
<td>☐ None requested 7/23/15, 7/27/15, 9/6/15</td>
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<tr>
<td>Clinical Microbiology</td>
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<td>Clinical Microbiology Team Leader Review(s) (indicate date for each review)</td>
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<td>Clinical Microbiology Review(s) (indicate date for each review)</td>
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<td>Biostatistics</td>
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<td>Statistical Team Leader Review(s) (indicate date for each review)</td>
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<td>Statistical Review(s) (indicate date for each review)</td>
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### Clinical Pharmacology
- **Clinical Pharmacology Division Director Review(s)** (indicate date for each review): No separate review
- **Clinical Pharmacology Team Leader Review(s)** (indicate date for each review): No separate review
- **Clinical Pharmacology review(s)** (indicate date for each review): None
- **OSI Clinical Pharmacology Inspection Review Summary** (include copies of OSI letters): None requested

### Nonclinical
- **Pharmacology/Toxicology Discipline Reviews**
  - ADP/T Review(s) (indicate date for each review): October 16, 2015
  - Supervisory Review(s) (indicate date for each review): September 29, 2015
  - Pharm/tox review(s), including referenced IND reviews (indicate date for each review): September 22, 2015
- **Review(s) by other disciplines/divisions/Centers requested by P/T reviewer** (indicate date for each review): None
- **Statistical review(s) of carcinogenicity studies** (indicate date for each review): No carc
- **ECAC/CAC report/memo of meeting**: Included in P/T review, page
- **OSI Nonclinical Inspection Review Summary** (include copies of OSI letters): None requested

### Product Quality
- **Product Quality Discipline Reviews**
  - Tertiary review (indicate date for each review): None
  - Secondary review (e.g., Branch Chief) (indicate date for each review): None
  - Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review): October 7, 2016
  - September 25, 2015
  - September 8, 2015
  - May 10, 2015
- **Reviews by other disciplines/divisions/Centers requested by product quality review team** (indicate date of each review): None
- **Environmental Assessment (check one)** (original and supplemental applications)
  - Categorical Exclusion (indicate review date: all original applications and all efficacy supplements that could increase the patient population): September 14, 2015
  - Review & FONSI (indicate date of review)
  - Review & Environmental Impact Statement (indicate date of each review)
- **Facilities Review/Inspection**
  - Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change): Acceptable
    - Re-evaluation date:
    - Withhold recommendation:
    - Not applicable
### Day of Approval Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td>No changes</td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
<td>Done</td>
</tr>
<tr>
<td>For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
<td>Done</td>
</tr>
<tr>
<td>For products that need to be added to the flush list (generally opioids): Flus List</td>
<td>Done</td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td>Done</td>
</tr>
<tr>
<td>If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td>Done</td>
</tr>
<tr>
<td>Ensure that proprietary name, if any, and established name are listed in the <em>Application Product Names</em> section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td>Done</td>
</tr>
<tr>
<td>Ensure Pediatric Record is accurate</td>
<td>Done</td>
</tr>
<tr>
<td>Send approval email within one business day to CDER-APPROVALS</td>
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/s/

AYANNA S AUGUSTUS
04/26/2016

PARINDA JANI
04/26/2016
Dear Jack,

Please find attached the current revised PI for Xtampza ER, which includes the revisions discussed during today’s call. Please provide a response (marked-up labeling) or indicate agreement with the Division’s edits as soon as possible.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

Reference ID: 3922902
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/s/

AYANNA S AUGUSTUS
04/26/2016
Dear Jack,

Please find attached the Division’s revisions to the current draft label for Xtampza ER. Please note that additional modifications to the label may occur on Monday.

Please review.

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
04/22/2016
Dear Jack,

I need to correct the information provided in my previous email regarding the abuse deterrent PMRs. As previously mentioned, the Division will be including a draft protocol submission milestone date for the two abuse deterrent. Please also note that the timelines for submitting the final protocol, study completion and final study report submission dates have been adjusted to accommodate additional time being added for protocol development and review. The revised timeline is below.

**PMR XXXX-1**
- **Draft Protocol Submission:** xx/xxxx (4 months after approval)
- Final Protocol Submission: XX/XXXX (8 months after approval)
- Study Completion: XX/XXXX (20 months after approval)
- Final Report Submission: XX/XXXX (2 years and 2 months after approval)

**PMR XXXX-2**
- **Draft Protocol Submission:** xx/xxxx (2 years and 4 months after approval)
- Final Protocol Submission: XX/XXXX (2 years and 8 months after approval)
- Study Completion: XX/XXXX (4 years and 8 months after approval)
- Final Report Submission: XX/XXXX (5 years and two months after approval)

Please confirm receipt of this email.

Regards,

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
two abuse deterrent PMRs described in my email dated March 29, 2016 (see below). The dates for both PMRs will be four months from the date of approval. The addition of this draft protocol submission date will facilitate adherence to the milestone schedule.

Please acknowledge receipt of this email and let me know if you have any questions.

Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

From: Augustus, Ayanna
Sent: Tuesday, March 29, 2016 10:20 AM
To: Jack Weet
Cc: Augustus, Ayanna
Subject: RE: Xtampza ER/Additional PMRs

Dear Jack,

Collegium will also be required to complete the following additional PMR studies to demonstrate the effectiveness of Xtampza ER’s abuse deterrent characteristics.

**PMR XXXX-1**
In order to provide the baseline data to support the hypothesis-testing studies required under PMR XXXX-2 (listed below), conduct a descriptive study that analyzes data on the following:

1) utilization of XTAMPZA ER (oxycodone extended release capsules) and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND

2) abuse of XTAMPZA ER (oxycodone extended release capsules) and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for XTAMPZA ER (oxycodone extended release capsules) as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.
- Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly
estimates) and calculate utilization-adjusted outcome estimates where possible.

This study will be conducted according to the following schedule:

Draft Protocol Submission: xx/xxxx (4 months after approval)
Final Protocol Submission: XX/XXXX (6 months after approval)
Study Completion: XX/XXXX (18 months after approval)
Final Report Submission: XX/XXXX (2 years after approval)

PMR XXXX-2
Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of XTAMPZA ER (oxycodone extended release capsules) actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of XTAMPZA ER (oxycodone extended release capsules) and should incorporate recommendations contained in Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA’s Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

This study will be conducted according to the following schedule:

Draft Protocol Submission: xx/xxxx (4 months after approval)
Final Protocol Submission: XX/XXXX (2.5 years after approval)
Study Completion: XX/XXXX (4.5 years after approval)
Final Report Submission: XX/XXXX (5 years after approval)

Let me know if you have any questions.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Tuesday, March 15, 2016 3:43 PM
To: Jack Weet <jweet@collegiumpharma.com>
Hi Jack,

Attached is a PDF copy of the acknowledgment letter for the request for final approval submission.

Also, below are the current ER/LA class PMRs for which timelines are already established:

**3033-1** A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.

b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

**PMR Schedule Milestones:**

<table>
<thead>
<tr>
<th>Final Protocol Submission:</th>
<th>11/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim Report (Cumulative Enrollment of 470 patients)</td>
<td>5/2017</td>
</tr>
<tr>
<td>Interim Report (Cumulative Enrollment of 1,042 patients)</td>
<td>9/2017</td>
</tr>
<tr>
<td>Interim Report (Cumulative Enrollment of 1,609 patients)</td>
<td>1/2018</td>
</tr>
<tr>
<td>Interim Report (Cumulative Enrollment of 2,300 patients)</td>
<td>6/2018</td>
</tr>
<tr>
<td>Study Completion:</td>
<td></td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td></td>
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</tbody>
</table>

**3033-2** An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

**PMR Schedule Milestones:**

<table>
<thead>
<tr>
<th>Final Protocol Submission:</th>
<th>11/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Completion:</td>
<td></td>
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</tbody>
</table>

Reference ID: 3921513
3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

PMR Schedule Milestones:

- Final Protocol Submission: 04/2015
- Study Completion: 10/2015
- Final Report Submission: 01/2016

3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

PMR Schedule Milestones:

- Final Protocol Submission: 04/2015
- Study Completion: 10/2016
- Final Report Submission: 02/2017

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioids for chronic pain.

PMR Schedule Milestones:

- Final Protocol Submission: 04/2015
- Study Completion: 12/2016
- Final Report Submission: 05/2017

3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

PMR Schedule Milestones:

- Final Protocol Submission: 11/2014
- Study Completion: 09/2016
- Final Report Submission: 12/2016

3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

PMR Schedule Milestones:

- Final Protocol Submission: 11/2014
- Study Completion: 10/2016
- Final Report Submission: 01/2017

3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.

PMR Schedule Milestones:

- Final Protocol Submission: 03/2015
- Study Completion: 10/2017
- Final Report Submission: 01/2018

3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.

Reference ID: 3921513
PMR Schedule Milestones: Final Protocol Submission: 03/2015
Study Completion: 09/2018
Final Report Submission: 12/2018

**3033-10** An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

PMR Schedule Milestones: Final Protocol Submission: 03/2015
Study Completion: 03/2017
Final Report Submission: 06/2017

**3033-11** Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.

Trial Completion: 02/2019
Final Report Submission: 08/2019

Let me know if you have any questions.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

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AYANNA S AUGUSTUS
04/22/2016
Thank you for your request, Ayanna.

I’ve consulted with Clinical Development, and have the following clarification:

“Single-treatment means that each subject will receive only oxycodone DETERx to treat his/her chronic pain – the maintenance or background pain.

Does this help to clarify? The note I got from Clin Dev went on to explain that if, for example, a study were to be examining two or more drugs at the same time, that the protocol would be designated as a two- or three- treatment study. I was asked to additionally clarify that single-treatment does not mean single-dose.

Please call me if this is still not clear. As this looks like a PREA PMR, I want to make sure that the language is clearly understood and articulated.

Thanks again and regards,

Jack
John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.828.4697
Mobile: [Redacted]
Main Tel.: 781.713.3699
jweet@collegiumpharma.com

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Thursday, April 21, 2016 9:24 AM
To: Jack Weet <jweet@collegiumpharma.com>
Subject: Xtampza ER/Pediatric Studies

Dear Jack,

The clinical team request clarification on the description of the pediatric studies that will be conducted for Xtampza ER. Specifically, clarify what is meant by “single-treatment”

“Conduct an open-label, single- and multiple-dose, [single-treatment], multi-center study to evaluate the pharmacokinetics and safety of XTAMPZA ER (oxycodone) extended-release capsules in patients... “
Please provide a response as soon as possible.

Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

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/s/

AYANNA S AUGUSTUS
04/21/2016
Dear Jack,

Please find attached the revised draft labeling for Xtampza ER. As previously communicated in my email sent on March 24, 2016, the Division has incorporated the opioid class safety labeling changes issued on March 22nd into this draft label.

Please review and provide a response (revised label in both clean and tracked changes) to the Division by COB, Thursday, April 14, 2016.

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

Reference ID: 3916264
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/s/

AYANNA S AUGUSTUS
04/12/2016
INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: John F. Weet
Vice President, Regulatory Affairs and Quality Assurance
780 Dedham Street - Suite 800
Canton, MA 02021

Dear Dr. Weet,

Please refer to your New Drug Application (NDA) dated and received December 12, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xtampza® (Oxycodone) extended-release capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We also refer to your submissions dated and received February 17, 2016; dated and received February 25, 2016; dated and received March 15, 2016; and dated and received March 18, 2016.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by Thursday, April 14, 2016.

1. Please commit to providing particle size distribution data from your validation batches including an analysis of variability. If significant variability is observed, please propose modifications to process or controls to address this variability. The FDA would like the opportunity to review the particle size distribution data and analysis prior to release of the batches.

These data and analysis should be provided to the application as a Special Report (21 CFR 314.81(b)(3)(ii)), referencing this Information Request letter.

2. Please commit to providing the dissolution data for all 5 strengths of Xtampza ER produced during process validation as outlined in Module 3.2.P.3.5.

Reference ID: 3926800
3. (b)(4)

If you have any questions, please contact Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 420-2773.

Sincerely,

Eric P. Duffy -A

Eric Duffy, Ph.D.
Director
Division of New Drug Products II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Jack,

As you know, based on your communications with the RPC, the ER/LA REMS materials have been revised. Please submit the following by COB, Friday, April 8th.

1. Word format with track changes
   a. REMS document and REMS appended materials (as a single document)
   b. REMS supporting document

2. PDF format clean documents (without track changes)
   a. REMS document and REMS appended materials (as a single document)
   b. REMS appended materials (as separate documents)
      i. Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics
      ii. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
      iii. Prescriber Letter 1
      iv. Prescriber Letter 2
      v. Prescriber Letter 3
      vi. Professional Organization/Licensing Board Letter 1
      vii. Professional Organization/Licensing Board Letter 2
      viii. ER/LA Opioid Analgesic REMS website (www.ER-LA-opioidREMS.com)*
   c. REMS supporting document

*The Agency understands that the website can only be submitted in PDF format.

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

---

Thank you, Ayanna. I’ve advised the team. I would anticipate that the addition of the class labeling would closely follow the language in the March 22 Communication.

We also note through our communication with RPC that there is yet again a revised REMS that is
being distributed to the RPC member companies. I would anticipate, however, that before we jump
the gun on that, that you provide us with an IR to amend the NDA accordingly.
Please advise.

Thanks and regards,

Jack
John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.828.4697
Mobile: (b) (6)
Main Tel.: 781.713.3699
jweet@collegiumpharma.com
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/s/

AYANNA S AUGUSTUS
04/05/2016
**Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)**

**BACKGROUND**

Please check all that apply: [ ] Full Waiver [x] Partial Waiver [ ] Pediatric Assessment [x] Deferral/Pediatric Plan

BLA/NDA#: 208090

PRODUCT PROPRIETARY NAME: Xstampza ER  ESTABLISHED/Generic NAME: oxycodone extended-release capsules

APPLICANT/SPONSOR: Collegium Pharmaceutical

**PREVIOUSLY APPROVED INDICATION/S:**

(1) ________________________________
(2) ________________________________
(3) ________________________________
(4) ________________________________

**PROPOSED INDICATION/S:**

(1) Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

(2) ________________________________
(3) ________________________________
(4) ________________________________

BLA/NDA STAMP DATE: 12 Dec 2014

PDUFA GOAL DATE: October 9, 2015

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:
Does this application provide for (If yes, please check all categories that apply and proceed to the next question):
NEW □ active ingredient(s) (includes new combination); □ indication(s); ☒ dosage form; ☒ dosing regimen; or □ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☒ No □

Did FDA confirm its agreement to the sponsor’s Agreed iPSP? Yes ☒ No □

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)
Yes ☒ No □

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes □ No ☒
If Yes, PMR #__________ NDA #__________
Does the division agree that this is a complete response to the PMR? Yes □ No ☒
If Yes, to either question Please complete the Pediatric Assessment Template.
If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.
WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor’s proposed language, include the appropriate language under Question 4 in this form.
- Pediatric Record

1. Pediatric age group(s) to be waived. Ages 0-2 yrs

2. Reason(s) for waiving pediatric assessment requirements (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as “Not Feasible.”) If applicable, chose from the adult-related conditions on the next page.

- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (This reason is for Partial Waivers Only)
3. Provide justification for Waiver:
There are too few patients below the age of 2 with chronic pain who would require an extended-release opioid around-the-clock for an extended period of time.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor’s proposed language:
   Sponsor’s proposed language is adequate
Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics
These conditions qualify for waiver because studies would be impossible or highly impractical.

- actinic keratosis
- adjunctive treatment of major depressive disorder
- age-related macular degeneration
- Alzheimer’s disease
- amyloidosis
- amyotrophic lateral sclerosis
- androgenic alopecia
- atherosclerotic cardiovascular disease
- autosomal dominant polycystic kidney disease (ADPKD)
- benign monoclonal gammopathy
- benign prostatic hyperplasia
- cancer:
  - basal cell and squamous cell skin cancer
  - bladder
  - breast
  - cervical
  - colorectal
  - endometrial
  - esophageal
  - follicular lymphoma
  - gastric
  - hairy cell leukemia
  - hepatocellular
  - indolent non-Hodgkin lymphoma
  - lung (small & non-small cell)
  - multiple myeloma
  - oropharynx (squamous cell)
  - ovarian (non-germ cell)
  - pancreatic
  - prostate
  - refractory advanced melanoma
  - renal cell
  - uterine
  - chronic lymphocytic leukemia
  - chronic obstructive pulmonary disease
  - cryoglobulinemia
  - diabetic peripheral neuropathy / macular edema
digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington’s chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson’s disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment
DEFERRAL REQUEST

Please attach:

☒ Pediatric Record

1. Age groups included in the deferral request: 2-7 and 7-17

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
The use of extended-release opioids for management of chronic pain is less common in children than in adults, and within the pediatric population, the prevalence of chronic pain generally increases with age. Based on available prevalence data, chronic pain is uncommon in younger children and becomes more common in older children and adolescents; only a subset of patients with chronic pain receives treatment with opioids. The report of the FDA’s scientific workshop on pediatric analgesic clinical trial design, measures, and extrapolation concludes that infants appear less likely than adults to develop chronic pain after similar types of nerve injury, and the frequency of recurrent pains generally increases with the onset of adolescence (Berde, 2012).

3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)

   a. Adult studies are completed and ready for approval for both age groups

4. Provide projected date for the submission of the pediatric assessment (deferral date):

5. Did applicant provide certification of grounds for deferring assessments? ☒ Yes ☐ No

6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? ☒ Yes ☐ No

SPONSOR’S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? ☒ Yes ☐ No
2. Does the division agree with the sponsor’s plan? ☑ Yes ☐ No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? ☑ Yes ☐ No

<table>
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<tr>
<th>Milestone</th>
<th>New Dates per FDA Request (March 2, 2016)</th>
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<tbody>
<tr>
<td><strong>PSP Timeline for ages 7 to &lt; 17</strong></td>
<td></td>
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<tr>
<td>Study Initiation</td>
<td>April 28, 2017</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>April 20, 2020</td>
</tr>
<tr>
<td><strong>PSP Timeline for ages 2 to &lt; 7</strong></td>
<td></td>
</tr>
<tr>
<td>Final Protocol CP-OXYDET-23 FDA Submission</td>
<td>October 31, 2018</td>
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<tr>
<td>Study Initiation</td>
<td>April 30, 2019</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>April 29, 2022</td>
</tr>
</tbody>
</table>

4. Has a Written Request been issued? ☐ Yes ☑ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted? ☐ Yes ☑ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.
DIVISION’S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

**Types of Studies/Study Design:**
For both age groups, the sponsor plans to conduct open-label safety and PK studies. Based on the mechanism of action of Xtampza and the similar exposure/response expected in children as in adults, efficacy can be extrapolated from the adult population.

**Nonclinical Studies:**
No additional nonclinical studies are required.

**Clinical Studies:**
The first study will be in pediatric patients ages 7-17, followed by the study in patients 2 to less than 7 years of age. Design of both studies will be similar.

**Age group and population (indication) in which study will be performed:**
See above.

**Number of patients to be studied or power of study to be achieved:**
Size of study will be based on number needed to provide adequate PK and safety information. Studies will not be powered because they are open-label.

**Entry criteria:**
Enrolled patients will be those who have severe enough pain to require daily, ATC opioid treatment for at least 14 days. These will be patients who would be eligible for ER opioid treatment even if not in the study.
**Clinical endpoints:**

- Exploratory pain intensity endpoints
- Safety endpoints
- Pharmacokinetic analyses

**Timing of assessments:**

- See details of protocol in PSP

**Division comments on product safety:**

- Are there any safety concerns currently being assessed? [ ] Yes  [x] No
- Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? [ ] Yes  [x] No
- Will a DSMB be required? [ ] Yes  [x] No

**Division comments on product efficacy:**

- Efficacy has been demonstrated in one AWC clinical trial in adults with chronic low back pain. Findings of efficacy in the adult population will be extrapolated to the pediatric population.

Reference ID: 3909697
Division comments on sponsor proposal to satisfy PREA:
The Division agrees with the sponsor’s proposal.

<table>
<thead>
<tr>
<th>PeRC ASSESSMENT TEMPLATE</th>
</tr>
</thead>
</table>

Please attach:

- [ ] Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.
- [ ] Pediatric Record

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC?  
[ ] Yes  [ ] No  If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

**Indication(s) that were studied:**
This section should list the indication(s) exactly as written in the **protocols**.

*Example:*

*DRUG for the treatment of the signs and symptoms of disease x.*

Number of Centers _____
| **Number and Names of Countries**
| ---

**Drug information:**

*Examples in italics*

- **Route of administration:** Oral
- **Formulation:** disintegrating tablet
- **Dosage:** 75 and 50 mg
- **Regimen:** list frequency of dosage administration

*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

**Types of Studies/Study Design:**

*Example:
Study 1: Multi-center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.
Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*

**Age group and population in which study/ies was/were performed:**

*Example:
Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients studied or power of study achieved:**

*Example:
Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.*
**Study 2:** powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients.

**Entry criteria:**
This section should list pertinent inclusion/exclusion criteria.

*Example:*
*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs*
*Patients had a negative pregnancy test if female.*

**Clinical endpoints:**

*Example:*
*Study 1: Clinical outcome and safety were the primary endpoints.*

*Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*

**Statistical information (statistical analyses of the data performed):**
This section should list the statistical tests conducted.

*Example:*
*Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control’s response rate.*

*Study 2: descriptive statistical methods for AUC, Cmax, Tmax, CL/F and compared to adults.*
### Timing of assessments:

*Example:*  
Baseline, week 2, week 6, and end of treatment

### Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
03/30/2016
Dear Jack,

Collegium will also be required to complete the following additional PMR studies to demonstrate the effectiveness of Xtampza ER’s abuse deterrent characteristics.

**PMR XXXX-1**
In order to provide the baseline data to support the hypothesis-testing studies required under PMR XXXX-2 (listed below), conduct a descriptive study that analyzes data on the following:

1) utilization of XTAMPZA ER (oxycodone extended release capsules) and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND

2) abuse of XTAMPZA ER (oxycodone extended release capsules) and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for XTAMPZA ER (oxycodone extended release capsules) as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

- Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

**This study will be conducted according to the following schedule:**

Final Protocol Submission: XX/XXXX (6 months after approval)
Study Completion: XX/XXXX (18 months after approval)
Final Report Submission: XX/XXXX (2 years after approval)

**PMR XXXX-2**
Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of XTAMPZA ER (oxycodone extended release capsules) actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of XTAMPZA ER (oxycodone extended release capsules) and should incorporate recommendations contained in Abuse-Deterrent Opioids—Evaluation and Labeling:

This study will be conducted according to the following schedule:

Final Protocol Submission: XX/XXXX (2.5 years after approval)
Study Completion: XX/XXXX (4.5 years after approval)
Final Report Submission: XX/XXXX (5 years after approval)

Let me know if you have any questions.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

Hi Jack,

Attached is a PDF copy of the acknowledgment letter for the request for final approval submission.

Also, below are the current ER/LA class PMRs for which timelines are already established.

3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.

b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with
long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

PMR Schedule Milestones:
Final Protocol Submission: 11/2015
Interim Report (Cumulative Enrollment of 470 patients) 5/2017
Interim Report (Cumulative Enrollment of 1,042 patients) 9/2017
Interim Report (Cumulative Enrollment of 1,609 patients) 1/2018
Interim Report (Cumulative Enrollment of 2,300 patients) 6/2018
Interim Report (Cumulative Enrollment of 2,300 patients) 10/2019
Study Completion:
Final Report Submission:

**3033-2** An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

PMR Schedule Milestones:
Final Protocol Submission: 11/2014
Study Completion: 4/2019
Final Report Submission: 9/2019

**3033-3** A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

PMR Schedule Milestones:
Final Protocol Submission: 04/2015
Study Completion: 10/2015
Final Report Submission: 02/2016

**3033-4** An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

PMR Schedule Milestones:
Final Protocol Submission: 04/2015
Study Completion: 10/2016
Final Report Submission: 02/2017

**3033-5** An observational study to validate measures of prescription opioid Substance Use Disorder
and addiction in patients who have received or are receiving opioids for chronic pain.

PMR Schedule Milestones: Final Protocol Submission: 04/2015
Study Completion: 12/2016
Final Report Submission: 05/2017

3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.
Study Completion: 09/2016
Final Report Submission: 12/2016

3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.
Study Completion: 10/2016
Final Report Submission: 01/2017

3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.
PMR Schedule Milestones: Final Protocol Submission: 03/2015
Study Completion: 10/2017
Final Report Submission: 01/2018

3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.
PMR Schedule Milestones: Final Protocol Submission: 03/2015
Study Completion: 09/2018
Final Report Submission: 12/2018

3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.
PMR Schedule Milestones: Final Protocol Submission: 03/2015
Study Completion: 03/2017
Final Report Submission: 06/2017

3033-11 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.
Trial Completion: 02/2019
Final Report Submission: 08/2019

Let me know if you have any questions.
Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
03/30/2016
NDA 208090

INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: John F. Weet
Vice President, Regulatory Affairs and Quality Assurance
780 Dedham Street-Suite 800
Canton, MA 02021

Dear Dr. Weet,

Please refer to your New Drug Application (NDA) dated and received December 12, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xstampza® (Oxycodone) extended-release capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We also refer to your Request for Final Approval dated and received February 29, 2016 and to your CMC Amendment NDA 208090, SN 0050, dated and received February 17, 2016.

We are reviewing NDA 208090, SN 0050 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by Monday, April 4, 2016.

You have submitted data

Submit data for dissolution profile comparisons between \textsuperscript{[b]} \textsuperscript{[e]} kg (biobatch) and \textsuperscript{[b]} \textsuperscript{[e]} kg scales product for oxycodone extended-release capsules.
If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Steven Kinsley
-A

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208090

INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: John F. Weet
Vice President, Regulatory Affairs and Quality Assurance
780 Dedham Street-Suite 800
Canton, MA 02021

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We also refer to your Request for Final Approval dated and received February 29, 2016 and to your CMC Amendment NDA 208090, SN 0050, dated and received February 17, 2016.

We are reviewing NDA 208090, SN 0050 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by Wednesday, March 16, 2016.

The manufacturing of commercial batch was submitted in an earlier submission. The justification and explanation of these variations has not been provided.

The relationship has not been established.

In order to fully understand the commercial manufacturing process and to assure that this process can be used to manufacture high quality drug product
consistently at the commercial scale, please provide [redacted] 

- Results of a study [redacted]

- [redacted] batch release data along with their executed batch records for all three validation batches.

If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Steven Kinsley

- A

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208090

Collegium Pharmaceuticals, Inc.
780 Dedham Street
Suite 800
Canton, MA 02021

Attention: Jack Weet, PhD
Vice President, Regulatory Affairs and Quality Assurance

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) dated and received December 12, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for XTAMPZA ER (oxycodone) extended-release Capsules: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We also refer to our tentative approval letter dated November 6, 2015, which contained the following error: inclusion of a patent that is not listed in the Orange Book.

This replacement tentative approval letter incorporates the correction of the error. The effective tentative approval date will remain November 6, 2015, the date of the original tentative approval letter.

We acknowledge receipt of your amendments dated December 17, 18, and 30, 2015, January 21, February 6, 11, and 23, March 6 (2), 11, 18 (2) and 24, April 6, 17, and 24, May 1, 15, and 28, June 8, and 16, July 8, 24, and 29, August 3,7(2), 10, 11, and 26, September 2, 22(2), 23, 24, and 25, and October 2, 5(2), 6, 7, 13, 14, 15, and 26, November 2, and 3, 2015.

This new drug application provides for the use of XTAMPZA ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the amended enclosed labeling text for the package insert, Medication Guide, and immediate container labels submitted October 5, 2015. This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Reference ID: 3857597
The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under Section 505(c)(3) of the FDCA [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to each of the patents under Section 505(b)(2)(A)(iv) of the FDCA stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application (“Paragraph IV certifications”).

Section 505(c)(3)(C) of the FDCA provides that approval of a new drug application submitted pursuant to Section 505(b)(2) of the FDCA shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under Section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of Section 505(b)(3) of the FDCA.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 7,674,799, 7,674,800, and 7,683,072, in the United States District Court for the District of Delaware. Therefore, final approval cannot be granted until:

1. a. Expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or

b. The date the court decides that the patents are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii) or (iv) of the Act, or,

c. The listed patents have expired, and

2. We are assured there is no new information that would affect whether final approval should be granted.¹

To obtain final approval of this application, submit an amendment two or six months prior to the: 1) expiration of the patent(s) and/or exclusivity protection or 2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as “REQUEST FOR FINAL APPROVAL”. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under

¹ We need not determine at this time whether approval of your 505(b)(2) NDA for XTAMPZA ER would otherwise be blocked by any other drug’s marketing exclusivity expiring before termination of the 30-month stay.
which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the FDCA and 21 U.S.C. 331(d).

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess the known serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which, upon full approval, XTAMPZA ER (oxycodone extended-release) will be a member;

- Identify an unexpected risk of serious systemic histopathological changes, teratogenicity, serious embryo-fetal developmental, and/or post-natal developmental adverse events, or cancer due to chronic exposure to the excipients myristic acid, beeswax, and carnauba wax in XTAMPZA ER or contaminants in the beeswax used to manufacture the drug product.

Furthermore, the new pharmacovigilance system that FDA is required to establish under Section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.
Therefore, based on appropriate scientific data, FDA has determined that if your application is approved, you will be required to participate in the conduct of the following postmarketing studies that have been required for all the ER/LA opioid analgesics:

- One or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

- Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

- Development and validation of measures for the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for the first PMR above and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

- A study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for the first PMR above.

Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for the first PMR above.

Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product
information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate.

If this application is approved, we encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies to provide the best information possible.

In addition, if this application is approved, you will be required to conduct the following individual postmarketing studies of XTAMPZA ER (oxycodone extended-release) Capsules:

- An epidemiologic investigation to address whether the properties intended to deter misuse and abuse of XTAMPZA ER (oxycodone extended-release) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community.

- A chronic (6-month) repeat-dose general toxicology study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A chronic (9-month) repeat-dose general toxicology study in the dog model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A fertility and early embryonic development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- An embryo-fetal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- An embryo-fetal development study in the rabbit model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A pre- and post-natal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A carcinogenicity assessment in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A carcinogenicity assessment in the mouse model testing the mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

- A detailed analysis of the beeswax employed in your drug product for potential residual levels of environmental and apicultural sources of contaminants, based on a thorough review of the apicultural practices across the globe and known contaminants in wax. Provide full
validated analytical methods used for testing of the contaminants, including the level of
detection. Provide a justification of the safety levels of contaminants present and the need for
routine testing of the beeswax prior to use in the manufacture of the drug product.

- A study to characterize the levels of [b] in the drug product using a validated analytical
  method and propose a release specification to adequately control [b] in the drug product.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational
study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class
of ER/LA opioid analgesics. Therefore, based on appropriate scientific data, if this application is
approved, you will be required to participate in the conduct of

- A clinical trial to estimate the serious risk for the development of hyperalgesia
  following use of ER/LA opioid analgesics for at least one year to treat chronic pain.
  We strongly encourage you to use the same trial to assess the development of
tolerance following use of ER/LA opioid analgesics. Include an assessment of risk
relative to efficacy.

We encourage you to work together with the holders of other approved NDA applications for
ER/LA opioid analgesics on this clinical trial to provide the best information possible.

If this application is ultimately approved, submit the protocols to your IND 075786, with a cross
reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the
submission with the following wording in bold capital letters at the top of the first page of the
submission, as appropriate:

- REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)
- REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)
- REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and
mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that
the benefits of the drug outweigh the risks [Section 505-1(a)].

In accordance with Section 505-1 of FDCA, we have determined that a REMS is necessary for
extended-release and long-acting (ER/LA) opioid analgesics, including XTAMPZA ER, to
ensure that the benefits of the drug outweigh the risks of serious adverse outcomes (addiction,
unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Your proposed REMS, submitted on November 2, 2015, and appended to this letter, can be
approved with your application. The REMS consists of a Medication Guide, elements to assure
safe use, and a timetable for submission of assessments of the REMS.
We will review your proposed REMS to assure that it matches the approved shared system REMS before final approval of your application.

If your application is ultimately approved, your REMS must be fully operational before you introduce XTAMPZA ER into interstate commerce.

Because XTAMPZA ER, if ultimately approved, will be a member of the ER/LA Opioid Analgesic REMS, the assessment plan will be the same assessment plan required for the other products covered by this shared system.

If your application is ultimately approved, our letter of approval will provide the details of the assessment plan for XTAMPZA ER.

If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
  Content of Labeling
  Carton and Container Labeling
  REMS

84 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
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/s/

SHARON H HERTZ
11/06/2015
Hi Jack,

Attached is the marked-up label for Xtampza ER. Please review the Division’s comments. If there are no additional comments or revisions to the label please submit a clean WORD document to the NDA as soon as possible. However, if additional revisions/comments are made, please submit the label in both clean and tracked changes to the NDA by Monday, November 2nd.

Let me know if you have any questions.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
11/02/2015
Dear Jack,

DRISK has completed the review of the ER/LA Opioid Analgesic REMS document and appended materials submitted on October 15, 2015. DRISK has the following comments, below, in response to Collegium’s proposal, including redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials.

1. Please note the additional track changes and comments in the attached *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.

2. NOTE: On October 23, 2015, a new ER/LA product, Belbuca buccal film, was approved by the Agency with a revised ER/LA REMS. The attached ER/LA REMS materials includes Belbuca's product specific information in the Blueprint, Prescriber Letters and Website where noted. If approved, Xtampza's REMS must include Belbuca's product specific information.

3. The "Most Recent Modification" date on the REMS document must be "XX/XXXX" as indicated in the redlined, attached PDF REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.

4. Resubmission and Format Instructions:
   - Submit the revised proposed (1) ER/LA Opioid Analgesic REMS for Xtampza with all appended materials and (2) the REMS Supporting Document as 2 separate, clean MS Word documents.
   - Provide a MS Word document with track changes of all revised materials.
   - Submit the attached, PDF document which includes the ER/LA Opioid Analgesic REMS for Xtampza with all appended materials. (Note the “Most Recent Modification: XX/XXXX” and the date in the header in the Blueprint are redlined but the rest of the document has no redlines in it)

Please provide the requested material by COB, Monday, November 2, 2015.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
11/02/2015
Hi Jack,

Attached is the revised draft label. Embedded are comments from the Division titled “Note to Sponsor”. We will discuss the Division’s changes during the 2pm call.

Best,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
10/26/2015
PeRC Meeting Minutes
September 30, 2015

PeRC Members Attending:
Hari Cheryl Sachs
Linda Lewis
Gettie Audain
Lily Mulugeta
Thomas Smith
Shrikant Pagay (Did not review Xampza)
Barbara Buch
Daiva Shetty
Wiley Chambers
Mehaun Payne
George Greeley
Freda Cooner
Gregory Reaman
Michelle Roth-Cline
Peter Starke (Did not review)
Adrienne Horatko-Munoz (reviews only)
Ilkram Elayan
Shrikant Pagay
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<td>9:55</td>
<td>NDA 208090 Xtampza ER Agreed iPSP (Partial Waiver/Deferral/Plan)</td>
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<td>11:25</td>
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</tbody>
</table>
Xtampza ER with Agreed iPSP (Partial Waiver/Deferral/Plan)

- **Indication:** Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The division noted that this is an abuse deterrent formulation and there may be advantages of the product over other abuse-deterrent extended release oxycodone products.

- **PeRC Recommendations:**
  - The PeRC concurred with the sponsor's plan for a partial waiver in the 0 to <2 years of age group because studies are not feasible and deferral in patients 2-7 years of age and 7-17 years of age as in the sponsor’s Agreed iPSP.
  - PeRC recommended correcting the timeline dates which are transposed.
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/s/

MESHAUN L PAYNE
10/16/2015
Dear Jack,

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of the ER/LA Opioid Analgesic REMS document and appended materials submitted on July 24, 2015, and have the following comments:

1. The ER/LA Opioid Analgesic REMS Supporting document must be submitted to your application in order to take action on this NDA. The ER/LA Opioid Analgesic REMS Supporting document can be obtained from the ER/LA Opioid Analgesic REMS Program Companies (RPC).

2. Update the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics as described in the attached redlined document. Note this version is the most recently approved ER/LA Opioid Analgesic REMS approved on October 2, 2015 which includes Morphabond's ® product specific information. This document must be aligned with any changes, if any, made to the Xtampza ER Prescribing Information.

3. The "Most Recent Modification" date on the REMS document must be changed to "XX/XXXX" as indicated in the redlined, attached REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.

4. Resubmission and Format Instructions:
   
   a. Resubmission Requirements and Instructions: Submit the revised proposed ER/LA Opioid Analgesic REMS for Xtampza ER with appended 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.

   b. Format Request: As noted previously, please 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. Please also submit for the Agency’s review mocked up PDF versions of all the materials and webpages which show the intended layout and graphic design of each.
Attached is the redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document. Please submit the revised REMS to the NDA as soon as possible, but no later than Thursday, October 15, 2015.

Let me know if you have any questions.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
10/13/2015
Hi Jack,

Enclosed is the marked-up Xtampza ER label. If you would like to discuss the Division’s revisions please let me know as soon as possible. Please also provided, via email, your comments for discussion/clarification and the marked-up label (accepting those changes you agree to and including Collegium’s revisions) as soon as possible. Please also send a clean WORD version of the label.

Thanks,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/OEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
10/13/2015
Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply:

☐ Full Waiver  ☒ Partial Waiver  ☐ Pediatric Assessment  ☒ Deferral/Pediatric Plan

BLA/NDA#: 208090

PRODUCT PROPRIETARY NAME: Xstampza ER

ESTABLISHED/Generic NAME: oxycodone extended-release capsules

APPLICANT/SPONSOR: Collegium Pharmaceutical

PREVIOUSLY APPROVED INDICATION/S:

(1) ______________________________________

(2) ______________________________________

(3) ______________________________________

(4) ______________________________________

PROPOSED INDICATION/S:

(1) Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

(2) ______________________________________

(3) ______________________________________

(4) ______________________________________

BLA/NDA STAMP DATE: 12 Dec 2014

PDUFA GOAL DATE: October 9, 2015

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:
Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?

Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Did FDA confirm its agreement to the sponsor’s Agreed iPSP? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR #______ NDA #______

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☐

If Yes, to either question Please complete the Pediatric Assessment Template. If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.
WAIVER REQUEST

Please attach:

☒ Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor’s proposed language, include the appropriate language under Question 4 in this form.

☒ Pediatric Record

1 Pediatric age group(s) to be waived. Ages 0-2 yrs

2 Reason(s) for waiving pediatric assessment requirements (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARTTS record, this reason is captured as “Not Feasible.”) If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☐ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (This reason is for Partial Waivers Only)
3. Provide justification for Waiver:
There are too few patients below the age of 2 with chronic pain who would require an extended-release opioid around-the-clock for an extended period of time.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor’s proposed language:
Sponsor’s proposed language is adequate
Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics
These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis
adjunctive treatment of major depressive disorder
age-related macular degeneration
Alzheimer’s disease
amyloidosis
amyotrophic lateral sclerosis
androgenic alopecia
atherosclerotic cardiovascular disease
autosomal dominant polycystic kidney disease (ADPKD)
benign monoclonal gammopathy
benign prostatic hyperplasia
cancer:
  basal cell and squamous cell skin cancer
  bladder
  breast
  cervical
colorectal
dermatologic
diabetic peripheral neuropathy / macular edema
endometrial
esophageal
cancer (continued):
  follicular lymphoma
  gastric
  hairy cell leukemia
  hepatocellular
  indolent non-Hodgkin lymphoma
  lung (small & non-small cell)
multiple myeloma
oropharynx (squamous cell)
ovarian (non-germ cell)
pancreatic
prostate
refractory advanced melanoma
renal cell
uterine
chronic lymphocytic leukemia
chronic obstructive pulmonary disease
cryoglobulinemia
diabetic peripheral neuropathy / macular edema
digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington’s chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson’s disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation
psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment
DEFERRAL REQUEST

Please attach:
- Pediatric Record

1. Age groups included in the deferral request: 2-7 and 7-17

2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
The use of extended-release opioids for management of chronic pain is less common in children than in adults, and within the pediatric population, the prevalence of chronic pain generally increases with age. Based on available prevalence data, chronic pain is uncommon in younger children and becomes more common in older children and adolescents; only a subset of patients with chronic pain receives treatment with opioids. The report of the FDA’s scientific workshop on pediatric analgesic clinical trial design, measures, and extrapolation concludes that infants appear less likely than adults to develop chronic pain after similar types of nerve injury, and the frequency of recurrent pains generally increases with the onset of adolescence (Berde, 2012).

3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)
   a. Adult studies are completed and ready for approval for both age groups

4. Provide projected date for the submission of the pediatric assessment (deferral date):

5. Did applicant provide certification of grounds for deferring assessments? ☒ Yes ☐ No

6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? ☒ Yes ☐ No

SPONSOR’S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? ☒ Yes ☐ No
2. Does the division agree with the sponsor’s plan? ☒ Yes ☐ No

3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)? ☒ Yes ☐ No

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<td></td>
</tr>
<tr>
<td>Final Protocol CP-OXYDET-22 FDA Submission</td>
<td>Friday, April 29, 2016</td>
</tr>
<tr>
<td>Study Initiation</td>
<td>Monday, October 31, 2016</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>Thursday, October 31, 2019</td>
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<tr>
<td><strong>PSP Timeline for ages 2 to &lt; 7</strong></td>
<td></td>
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<tr>
<td>Final Protocol CP-OXYDET-23 FDA Submission</td>
<td>Monday, April 30, 2018</td>
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<tr>
<td>Study Initiation</td>
<td>Wednesday, October 31, 2018</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>Friday, October 29, 2021</td>
</tr>
</tbody>
</table>

4. Has a Written Request been issued? ☐ Yes ☒ No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

5. Has a PPSR been submitted? ☐ Yes ☒ No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

*Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.*
DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:
For both age groups, the sponsor plans to conduct open-label safety and PK studies. Based on the mechanism of action of Xtampza and the similar exposure/response expected in children as in adults, efficacy can be extrapolated from the adult population.

Nonclinical Studies:
No additional nonclinical studies are required.

Clinical Studies:
The first study will be in pediatric patients ages 7-17, followed by the study in patients 2 to less than 7 years of age. Design of both studies will be similar.

Age group and population (indication) in which study will be performed:
See above

Number of patients to be studied or power of study to be achieved:
Size of study will be based on number needed to provide adequate PK and safety information. Studies will not be powered because they are open-label.

Entry criteria:
Enrolled patients will be those who have severe enough pain to require daily, ATC opioid treatment for at least 14 days. These will be patients who would be eligible for ER opioid treatment even if not in the study.
Clinical endpoints:

Exploratory pain intensity endpoints
Safety endpoints
Pharmacokinetic analyses

Timing of assessments:

See details of protocol in PSP

Division comments on product safety:

Are there any safety concerns currently being assessed? ☐ Yes ☒ No

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? ☐ Yes ☒ No

Will a DSMB be required? ☐ Yes ☒ No

Other comments:

Division comments on product efficacy:

Efficacy has been demonstrated in one AWC clinical trial in adults with chronic low back pain. Findings of efficacy in the adult population will be extrapolated to the pediatric population.
Division comments on sponsor proposal to satisfy PREA:
The Division agrees with the sponsor’s proposal.

PeRC ASSESSMENT TEMPLATE

Please attach:

☐ Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.

☐ Pediatric Record

Date of PREA PMR:

Description of PREA PMR: (Description from the PMC database is acceptable)

Was Plan Reviewed by PeRC? ☐ Yes ☐ No  If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:
This section should list the indication(s) exactly as written in the protocols.

Example:
DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____
Drug information:

Examples in italics

- **Route of administration**: Oral
- **Formulation**: disintegrating tablet
- **Dosage**: 75 and 50 mg
- **Regimen**: list frequency of dosage administration

*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/Study Design:

Example:

Study 1: Multi-center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study(ies) was/were performed:

Example:

Study 1: patients aged X to Y years.
Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.
**Study 2**: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients.

**Entry criteria:**
This section should list pertinent inclusion/exclusion criteria.

*Example:*
**Entry criteria:** Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients had a negative pregnancy test if female.

**Clinical endpoints:**

*Example:*
**Study 1:** Clinical outcome and safety were the primary endpoints.

**Study 2:** The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

**Statistical information (statistical analyses of the data performed):**
This section should list the statistical tests conducted.

*Example:*
**Study 1** - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control’s response rate.

**Study 2**: descriptive statistical methods for AUC, Cmax, Tmax, CL/F and compared to adults.
### Timing of assessments:
*Example:*
Baseline, week 2, week 6, and end of treatment

### Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.
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/s/

AYANNA S AUGUSTUS
10/08/2015
Dear Jack,

Please provide an amendment to NDA 208090 that you will commit to only manufacturing the registration batch scale of \[80\] Kg and will provide commercial scale information in a Prior Approval Supplement.

Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
10/02/2015
Dear Jack,

Enclosed is the list of PMRs discussed during today’s call. For each PMR we will need the following:

| Final Protocol Submission Date: | MM/DD/YYYY |
| Study/Trial Completion: | MM/DD/YYYY |
| Final Report Submission: | MM/DD/YYYY |

1. Conduct a chronic (6-month) repeat-dose general toxicology study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

2. Conduct a chronic (9-month) repeat-dose general toxicology study in the dog model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

3. Conduct a fertility and early embryonic development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

4. Conduct an embryo-fetal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

5. Conduct an embryo-fetal development study in the rabbit model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

6. Conduct a pre- and post-natal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

7. Conduct a carcinogenicity assessment in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

8. Conduct a carcinogenicity assessment in the mouse model testing the mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.
9. Complete a detailed analysis of the beeswax employed in your drug product for potential residual levels of environmental and apicultural sources of contaminants, based on a thorough review of the apicultural practices across the globe and known contaminants in wax. Provide full validated analytical methods used for testing of the contaminants, including the level of detection. Provide a justification of the safety levels of contaminants present and the need for routine testing of the beeswax prior to use in the manufacture of the drug product.

In addition, please provide a timeline for the CMC post-marketing requirement discussed regarding the drug product specification.

10. Conduct a study to characterize the levels of [formaldehyde] in the drug product and propose a release specification to adequately control [formaldehyde] in the drug product.

Please provide timelines, via email, for these PMRs as soon as possible. The review team will review your proposals and provide comments before submission of the final timelines to the NDA. Please also be sure to submit to the NDA, as soon as possible, your proposal to set specifications in the carnauba wax, beeswax and myristic acid.

We also remind you of the ER/LA opioid class PMRs for which the milestones have already been specified at the time the study requirements were issued for the class of ER/LA opioid analgesics.

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited
to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: 08/2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR #2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR #2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: 08/2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR #2065-1.

The following timetable proposes the schedule by which you will conduct this study:
2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission: 08/2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

Finally, here is the list of meeting attendees:

Sharon Hertz, MD Director
Ellen Fields, MD, Deputy Director
Dan Mellon, PhD, Pharmacology/Toxicology Supervisor
Grace Lee, PhD, Pharmacology/Toxicology Reviewer
Ciby Abraham PhD, Acting Quality Assessment Lead
Julia Pinto, PhD, Acting Branch Chief

Let me know if you have any questions.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
10/02/2015
Hi Jack,

Please see the following response to your question.

The CMC review team also has the following additional comments/revision for the immediate container labels.

1. Remove [b (4)]
2. Bottom right corner of the label should state: Manufactured by: company name and address
3. Place “NDC” under the barcode.

We acknowledge that you may not be able to provide mock-ups of the revised container labels by Friday, therefore please provide these as soon as possible.

In addition, the Division would like to schedule a teleconference for Thursday at 3:00 PM. Please confirm availability for this tcon and provide a call-in number and list of meeting attendees. The Division would like to discuss the drug product spec for Pb. Please include product quality and nonclinical team members on the call.

Best,
Ayanna
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/s/

AYANNA S AUGUSTUS
10/02/2015
HI Jack,

Here is the information request regarding the container labels:

We agree with your rationale to include the salt equivalency statement on the principal display panel (PDP). Relocate the full equivalency statement to appear on the PDP.

Consider removing the graphic above the proprietary name to make room for the full equivalency statement and to minimize distraction from the proprietary and established name (critical information).

Please provide mock-ups of the revised labels by COB, Friday, October 2nd.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
09/30/2015
Hi Jack,

Please see the following comments on the container labels for Xtampza.

A. Container Labels

1. Place the medication guide statement under the net quantity statement “100 capsules” on the principal display panel and consider making the font for the medication guide statement smaller to make room for the food effect statement in A.5 below.

2. Move the NDC number, proprietary name, established name, and strength up toward the top of the label to increase their prominence.

3. Remove

4. Move the salt equivalent statement “Equivalent to XX mg Oxycodone Hydrochloride” to the side panel to make additional room for the following food effect statement in A.5 below. Also, consider revising the format of the salt equivalent statement to the following if room permits:

   Each capsule contains:
   Oxycodone.....XX mg
   (equivalent to XX mg Oxycodone Hydrochloride USP)

5. Add the following food effect statement on the principal display panel directly below the strength to highlight the need to take with food:

   “Always take Xtampza ER with food. Taking on an empty stomach can decrease drug absorption”

   Additionally, use a bold red font and box the food effect statement as follows:
6. Relocate the dosage form to appear outside of the parenthesis and use title case to increase its prominence to mitigate potential confusion with other immediate release oral oxycodone products.

   For example:
   Xtampza ER
   (oxycodone) Extended-Release Capsules

7. Change the modifier ‘ER’ font to the same size as the capital letter ‘X’ in Xtampza to increase the prominence of the dosage form.

8. Decrease the font size of the CII symbol to ensure that the proprietary name, established name, and strength are the most prominent information on the label. Also, consider moving the symbol to the right to increase the white space between the proprietary name and the symbol.

Please submit revised container labeling by COB, Monday, September 28th. The Division is working on the package insert and will provide revised draft labeling as soon as possible.

Best,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/OI/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

Reference ID: 3822824
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/s/

AYANNA S AUGUSTUS
09/21/2015
Hi Jack,

The timelines proposed in the iPSP for the deferred pediatric studies are not specific enough and need to be revised to more specific dates (MM/DD/YYYY), not just the month and year for submission of the protocol, study initiation and final study report. In addition the iPSP indicates that you plan to submit the first study protocol for ages 7-17 years in Sept 2015. This will need to be pushed back by 6 months to allow the Agency time to review and negotiate the study protocol. The subsequent dates will need to be modified accordingly.

Please submit the revised timelines for all proposed pediatric studies to the NDA as soon as possible but no later than Wednesday, September 23rd.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
09/18/2015
Dear Jack,

The listed drug product referenced in your 505(b)(2) NDA has two new patents listed in the Orange book. Please submit the appropriate patent certification for these two patents to the NDA as soon as possible.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
09/18/2015
Dear Dr. Weet,

Please refer to your original New Drug Application received December 12, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DETERx® (Oxycodone) extended-release capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg strengths.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, September 22, 2015.

1. The conclusion you have submitted in amendment SN 0031 dated 8/26/2015 is not acceptable.

All registration batches were manufactured...
2. Provide the bulk lots and the finished products lot numbers for all the samples used to generate results for various hold studies (amendment SN0030 dated 8/11/2015).

3. FDA does not agree

4. Based on an evaluation of the IR Amendment SN0029 dated 8/10/2015 and inspectional findings, we find
If you have any questions, please contact me, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Steven Kinsley
-

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208090

INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: Jack Weet, Regulatory Affairs and Quality Assurance
780 Dedham Street
Suite 800
Canton, MA 02021

Dear Dr. Weet,

Please refer to your original New Drug Application received Friday, December 12, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xtampza ER® Oxycodone extended-release capsules in 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Tuesday, August 11, 2015.

1. Please submit revise table (table 11, Section 3.2.P.3.3.9) for Summary of Differences between Pilot and Commercial Scale Batch records” which include the information

2. Submit hold data for review for the following materials

Sincerely,

Steven Kinsley
- S

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Reference ID: 3926800
Dear Jack,

Please provide a response to the following CMC information requests by COB, Friday, August 7, 2015.

1. *The proposed acceptance limit for unspecified impurity in the drug product (NMT 0.04%) We do not agree*  

2. *The drug product method precision validation was said conducted Clarify*  
   
   *Then properly conducted precision and study results should be obtained and submitted to the NDA.*

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC  
Sr. Regulatory Health Project Manager  
FDA/CDER/OND/ODEII/DAAAP  
Fax: 301-796-9723  
Ph: 301-796-3980

Reference ID: 3802232
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/s/

AYANNA S AUGUSTUS
08/05/2015
NDA 208090

INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: John F. Weet, PhD, Regulatory Affairs and Quality Assurance
780 Dedham Street
Suite 800
Canton, MA 02021

Dear Dr. Weet,

Please refer to your original New Drug Application received Friday, December 12, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DETERx® Oxycodone extended-release capsules in 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Friday, August 10, 2015.

Provide details on the processing of both the beeswax and carnuba waxes, (6)b
Since the exact origin of the beeswax is unknown, provide justification that your assessment (6) is adequate to fully characterize the potential for all possible residual (6) that may be present.

Provide assurance that the beeswax used in the preparation of the drug product, does not contain protein allergens.

Sincerely,

Steven Kinsley - S

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Reference ID: 3926800
INFORMATION REQUEST

Collegium Pharmaceutical, Inc.
Attention: John F. Weet, PhD, Regulatory Affairs and Quality Assurance
780 Dedham Street
Suite 800
Canton, MA 02021

Dear Dr. Weet,

Please refer to your original New Drug Application received Friday, December 12, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxycodone ER capsules in 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your supplement. Please submit your response prior to COB Monday, August 3rd, 2015.

1. The data/information provided under “dissolution acceptance criteria justification” do not support your proposed criteria for dissolution. FDA recommends the implementation of the following dissolution acceptance criteria for your proposed product. Revise the criteria accordingly and submit the specifications table with the updated acceptance criteria for the dissolution test.

<table>
<thead>
<tr>
<th>Dissolution Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (40) % at 1 hour</td>
</tr>
<tr>
<td>50 (40) % at 4 hours</td>
</tr>
<tr>
<td>NLT 10% at 12 hours</td>
</tr>
</tbody>
</table>

If you have any questions, call Steven Kinsley, Regulatory Business Project Manager, at (240) 402-2773.

Sincerely,

Steven
Kinsley -S

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Jack,

Please provide a response to the following information request by COB, Friday, July 24th.

In the study report for CP-OXYDET-08, there is reference to subjects taking opioids in the double-blind phase “natural opium alkaloids were the most frequently reported (12.3% overall), and were used by more subjects in the placebo group (13.8%) than those in the Xtampza group (10.9%).” Subjects were supposed to receive APAP as rescue. Please clarify why subjects were taking additional opioids during the double-blind phase of your study and whether these were considered protocol violations.

Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980
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/s/

AYANNA S AUGUSTUS
07/22/2015
Dear Alison:

Please submit a complete REMS document for ERLA by COB 7/24/15. This includes the proposed REMS document, REMS materials, REMS supporting document, and Medication Guide. It should be based on the most recently approved REMS document (6/2015).

Regards

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/

-----------------------------------------------
AYANNA S AUGUSTUS
07/21/2015

Reference ID: 3795259
Hi Jack,

Thank you for your question. A t-con is not necessary at this time. Our response to your question is as follows:

"We acknowledge that the finished product release includes dissolution testing. Listed content uniformity and dissolution as part of release testing are adequate."

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773
1. Please add the following in Master batch record: (Section 3.2.P.3.: 3.8 Critical Processing Parameters Table 9

Collegium Response:

Related to [redacted] testing, please clarify what content uniformity, and dissolution testing you are requesting that we add. We currently include [redacted] content uniformity and dissolution as part of release testing. We would appreciate a 15-minute telecon at your earliest convenience to discuss this request.

Please reply at your earliest convenience. If possible, we would like to discuss this topic this week, in order to facilitate preparing a response to you by the July 29, 2015 deadline.

Jack
John F. Weet, PhD
Vice President
Regulatory Affairs and Quality Assurance
COLLEGIUM Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021
Tel.: 781.713.3731 | Fax.: 781.628.4697
Mobile: [redacted]
Main Tel.: 781.713.3699
jweet@collegiumpharma.com

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Dear Alison,

Please provide a response to the following clinical information request by COB, Wednesday, May 6, 2015.

1. On pages 103 and 106 of the summary of clinical safety, you stated 5 subjects had ongoing AEs who discontinued during the titration phase, as well as 3 subjects who had ongoing AEs who discontinued during the double-blind phase. Provide the subject numbers for these subjects so the corresponding narratives may be easily reviewed.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
04/30/2015
Dear Alison,

Please provide a response to the following clinical pharmacology information requests:

1. While reviewing the results of study CP-OXYDET-24, we noticed that several subjects receiving placebo (Treatment F) experienced drug liking/high during the “treatment phase”. To explain the observation possibly due to a treatment containing oxycodone, we have focused on blood levels of oxycodone in subjects receiving placebo (Treatment F). Subjects showing high drug liking (#24-261, 24-312, 24-325, 24-341, 24-24-392), i.e., above 61 in the bipolar scale, had no documentation of any plasma sample analysis from the placebo group. Whereas, these same subjects had plasma levels of oxycodone reported in other treatment groups (A-E). We also noticed that none of the subjects 24-356, 24-358, 24-369, 24-374, 24-385, 24-393, 24-398, 24-401, had any record of plasma sample analysis for oxycodone in the bioanalytical report or pc.xpt dataset.

Provide a response to the following:

a) Were blood samples collected after receiving Treatment F (placebo) from subjects (#24-261, 24-312, 24-325, 24-341, 24-24-392, 24-356, 24-358, 24-369, 24-374, 24-385, 24-393, 24-398, 24-401.)?

b) If blood samples were collected, provide bioanalytical data and revised pc.xpt dataset to include oxycodone levels from the above indicated subjects from Treatment F.

c) If blood samples were not collected or collected but not analyzed provide an explanation.

2. While reviewing study CP-OXYDET-21, we noticed that oxycodone PK data from subjects receiving placebo (Treatment D) was not provided in the pc.xpt dataset. We note that the protocol specifies that blood samples were collected from subjects after all treatments including Treatment D (placebo).

Provide a response to the following:

a) If blood samples were collected, provide bioanalytical data and revised pc.xpt dataset to include oxycodone levels from all subjects from Treatment D.

b) If blood samples were not collected or collected but not analyzed provide an explanation.

Please provide a response as soon as possible and let me know your timeframe for providing a response.

Reference ID: 3732745
Best Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
04/15/2015
Dear Alison,

The Division received the April 6th submission which contained responses to the comments/requests noted in the 74-day letter. Please also, let me know when the Division can expect to receive the 120-day safety update for Xtampza.

The nonclinical team request a response to the following information requests as soon as possible. Please let me know the expected timeframe for response to each of these requests.

The 90-day dog toxicity study of a beeswax/carnauba wax [Study No. 724003] is being reviewed and the following additional information is requested.

1. In the 90-day dog study, potential test article-related histology findings were observed in the following tissues: pancreas and mandibular salivary gland. Perform histological evaluation on these tissues for the low and mid dose groups of males and females, and provide historical control incidences for findings (mean and range) in these tissues from the testing laboratory. Particularly, we have more concern for the pancreatic findings as two dogs in the high dose group had multiple findings in the pancreas. Namely, one high dose male had minimal fibroplasia, mild single cell necrosis, minimal decreased zymogen granules, and minimal acinar cell hyperplasia, whereas one high dose female had minimal single cell necrosis, mild decreased zymogen granules, and minimal acinar atrophy. Provide an assessment of the toxicologic significance of these pancreatic findings.

2. In the 90-day dog study, analyses of the test article formulations and toxicokinetic parameters were not included. Furthermore, emesis findings were noted in all dose groups, with higher incidences in the control and high dose groups. Thus, it is unknown whether all dogs were adequately exposed to the test article as it was intended, and it cannot conclude that animals in the high dose group were exposed to a higher level of the test article than animals in the mid or low dose groups. Conduct histological evaluation on all tissues for the low and mid dose groups and revise the study report accordingly.

Best Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
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/s/

AYANNA S AUGUSTUS
04/13/2015
NDA 208090

Collegium Pharmaceuticals, Inc.
Attn: Alison Fleming, PhD
Vice President, Product Development
780 Dedham Street, Suite 800
Canton, MA 02021

Dear Dr. Fleming:

Please refer to your New Drug Application (NDA) dated December 12, 2014, received December 12, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xtampza ER (oxycodone extended-release) Capsules: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by May 4, 2015 in order to continue our evaluation of your NDA.

A. The Drug Product:

1. Revise the specifications to use a test specific for the API or two orthogonal identification tests per ICH Q6A.

2. The acceptance limit of NMT % total impurities for the drug product.

3. Drug product registration batch release results

4. The batch release data of capsule lot 3104074R reported

Reference ID: 3926800

1. In the manufacturing process development report, you stated

2. Please provide the batch analysis report for the following batches:

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

Ciby J. Abraham -A
Ciby J. Abraham, Ph.D.
Application Technical Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Dear Mike,

Please provide a response to the following information requests as soon as possible.

1. Provide Study CP-OXYDET-21’s datasets in ADaM format
2. Provide the SAS code of Pharmacodynamics statistical analysis for both studies CP-OXYDET-21 and CP-OXYDET-24.

Best Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980

Dear Ayanna,

I will be out of the office on vacation starting today (3/11) through Friday (3/13). I will be checking email, but may not see an important communication in a timely manner. I would appreciate if you would copy Mike Heffernan (copied on this email) on any requests you may have regarding NDA 208090 during this period.

Thank you!

Regards,
Alison
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/s/

AYANNA S AUGUSTUS
03/12/2015

Reference ID: 3715046
Dear Alison,

After reviewing the contents of this recent submission the reviewer is not able to located the needed PD datasets. The Pharmacodynamic dataset should include all of the parameters of interest that were collected in studies CP-OXYDET-24 and CP-OXYDET-21 such as Drug Liking, Overall (Global) Drug Liking, Take Drug Again, DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy), PVAQ, ARCI/MBG, Pupillometry etc.

Please provide a response as soon as possible or indicate where in the submission these datasets can be located.

Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
03/05/2015
From: Augustus, Ayanna
To: afleming@collegiumpharma.com
Cc: Augustus, Ayanna
Subject: RE: NDA 208,090, Question regarding Notice of Paragraph IV Certification- clarification
Date: Thursday, February 26, 2015 11:55:15 AM

Dear Alison,

I noticed that the patent certification submitted to the NDA does not contains certification for Patents 8894987 and 8894988 listed in the orange book for the RLD. Please submit updated patent certification for this NDA as soon as possible.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980

From: Alison Fleming [mailto:afleming@collegiumpharma.com]
Sent: Monday, February 09, 2015 3:31 PM
To: Augustus, Ayanna
Subject: RE: NDA 208,090, Question regarding Notice of Paragraph IV Certification- clarification

Excellent. Thank you.

From: Augustus, Ayanna [mailto:Ayanna.Augustus@fda.hhs.gov]
Sent: Monday, February 09, 2015 2:27 PM
To: afleming@collegiumpharma.com
Cc: Augustus, Ayanna
Subject: RE: NDA 208,090, Question regarding Notice of Paragraph IV Certification- clarification

Dear Alison,

Your proposal to use FedEx as an alternative means to document receipt of notice of the patent certification is acceptable.

Best Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980

From: Alison Fleming [mailto:afleming@collegiumpharma.com]
Sent: Monday, February 09, 2015 12:52 PM
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/s/

AYANNA S AUGUSTUS
02/26/2015
Dear Alison,

Attached is the 74-day letter for Xtampza, which list several review issues that need to be addressed as soon as possible. Please also provide a response to the following information request:

We are unable to locate the PD datasets for your NDA. Please indicate where these datasets are located in your submission or submit these to the NDA by COB, Thursday, March 5, 2015.

Best Regards,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
02/26/2015
Dear Dr. Fleming:

Please refer to your New Drug Application (NDA) dated December 12, 2014, received December 12, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xtampza ER (oxycodone extended-release) Capsules: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We also refer to your amendments dated December 17, 18, and 30, 2014, and January 21, February 6, and 11, 2015.

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 Standard. Therefore, the user fee goal date is October 12, 2015.

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 commitment requests by September 21, 2015. This date conforms to the 21st Century Review timeline for your application. If our review continues
on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

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

**Nonclinical**

1. Upon preliminary review, your NDA does not appear to contain adequate information to justify the safety of the drug product formulation. Specifically, a complete toxicity profile of beeswax was not included in your NDA submission. Submit the final study report of the 90-day dog study using beeswax and carnauba wax [Study Number 724003] as soon as possible; however, we cannot guarantee that this study will be reviewed during this review cycle, and submission of the final study report could impact the action date for this application. In addition, you do not appear to have provided a chronic toxicity profile of beeswax or chronic toxicity studies using saturated, unbranched long-chain free fatty acids. We also note that you provided only tertiary review articles containing only summary data for certain constituents of beeswax (e.g., toxicity studies using oleyl palmitate or Class I mineral oil). Provide copies of the original source materials (primary references) for these studies, if possible. As previously communicated, a final determination of the adequacy of the safety assessment of the novel excipients based on a detailed review of all submitted toxicological data (including reproductive and developmental toxicity and carcinogenicity data) will be made during the NDA review cycle, and inadequate toxicology data could be potentially approval issues.

2. Upon preliminary review, the proposed specification for unspecified impurity in the drug product (NMT [5%] [6%])

**Chemistry, Manufacturing, and Controls (CMC)**


**Biopharmaceutics**

1. There is no IVIVC approved for your proposed product. Therefore, the selection of the dissolution acceptance criteria limits should be based on the mean target (biobatches) value ± [6]% variation and NLT [4]% for the last specification time-point. Implement these acceptance criteria for your proposed product and provide the revised specifications table with the updated acceptance criteria for the dissolution test. Also, provide justification for the selected last specification time point (i.e., [6] h) when more than [4]% of the drug is released within 12 hours.
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.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in **UPPER CASE** letters. The headings should be in the center of a solid horizontal line, not a dashed line.

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
6. **Highlights Heading:** At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “HIGHLIGHTS OF PRESCRIBING INFORMATION”.

7. **Highlights Limitation Statement:** The **bolded** HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).” The name of drug product should appear in UPPER CASE letters. Be sure to include the proprietary name.

8. **Product Title in Highlights:** The product title must be **bolded**.

9. **Adverse Reactions in Highlights:** For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

10. **Revision Date in Highlights:** The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 9/2013”).

11. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.” Omit Section 15 if there aren’t any references included in the FPI.

12. The following heading must be **bolded** and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

13. All text should be **bolded** in the boxed warning.

14. The boxed warning must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one Warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the Warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”).


We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **March 18, 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Reference ID: 3707312
At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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](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 partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.
If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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/s/

SHARON H HERTZ
02/25/2015
Hi Alison,

Please provide a response to the following information request by 11am tomorrow, if possible.

Please confirm your intent for the ongoing 90-day repeat oral toxicology dog study testing the mixture of carnauba and beeswax that your submission indicates will be submitted to the NDA in March of 2015.

If this study was not able to be completed for submission to the NDA, do you believe that the existing literature-based safety justification for the excipients is adequate to support approval of your drug product formulation?

Best Regards,
Ayanna
Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
02/05/2015
Hi Alison,

We acknowledge your submission of case narratives of serious adverse events, severe adverse events and deaths within the CP-OXYDET-08 Clinical Study Report. However, you must also provide narratives for dropouts due to adverse events. Please indicate when these narratives will be submitted to the NDA for review.

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
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/s/

AYANNA S AUGUSTUS
02/02/2015
DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208090

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Collegium Pharmaceutical, Inc.
780 Dedham Street, Suite 800
Canton, MA 02021

ATTENTION: Michael T. Heffernan, RPh
President and CEO

Dear Mr. Heffernan:

Please refer to your New Drug Application (NDA), dated and received December 12, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Extended-Release Capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg.

We also refer to your correspondence, dated and received December 17, 2014, requesting review of your proposed proprietary name, Xtampza ER.

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

If any of the proposed product characteristics as stated in your December 17, 2014, 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 Ayanna Augustus, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3980.

Sincerely,

Todd Bridges, RPh
Deputy 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

Reference ID: 3695398
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/s/

TODD D BRIDGES
02/02/2015
Hi Alison,

Please provide an analysis of efficacy results by subgroups (gender, age, race, etc) for study OXDET-08. Please provide this information to us in tabular format or indicate where this information is located in the NDA submission by COB, Monday, January 19, 2015.

Best Regards,

Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980
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/s/

AYANNA S AUGUSTUS
01/20/2015

Reference ID: 3689747
NDA 208090

NDA/BLA ACKNOWLEDGMENT

Collegium Pharmaceuticals, Inc.
780 Dedham Street
Suite 800
Canton, MA 02021

Attention: Michael T. Heffernan, RPh
President and CEO

Dear Mr. Heffernan:

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: Xtampza ER (oxycodone extended-release) Capsules; 9 mg, 13.5mg, 18mg, 27 mg, 36 mg

Date of Application: December 12, 2014

Date of Receipt: December 12, 2014

Our Reference Number: 208090

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 February 10, 2015, 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).
Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, “Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank,” [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at [http://www.fda.gov/opacom/morechoices/fdaforms/default.html](http://www.fda.gov/opacom/morechoices/fdaforms/default.html).

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, “Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007,” that describes the Agency’s current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: [http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA ct/ SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/uc m095442.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA ct/ SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/uc m095442.htm). Additional information regarding Title VIII of FDAAA is available at: [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html). Additional information for registering your clinical trials is available at the Protocol Registration System website [http://prsinfo.clinicaltrials.gov/](http://prsinfo.clinicaltrials.gov/).

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208090** submitted on December 12, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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, contact me at (301) 796-3980 or ayanna.augustus@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D., RAC
Sr. 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/

AYANNA S AUGUSTUS
12/18/2014
Dear Dr. Fleming:

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

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2014. The purpose of the meeting was to discuss your NDA for Oxycodone DETERx.

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, MS
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 16, 2014; 3 PM EST
Meeting Location: 10906 New Hampshire Avenue
                  Bldg 22, Room 1377
                  Silver Spring, MD 20903

Application Number: IND 075786
Product Name: Oxycodone DETERx Capsules
Indication: management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Sponsor/Applicant Name: Collegium Pharmaceutical, Inc.

Meeting Chair: Sharon Hertz, MD
Meeting Recorder: Lisa Basham, MS

FDA ATTENDEES
Bob A. Rappaport, MD  Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Sharon Hertz, MD  Deputy Director, DAAAP
John Feeney, MD  Clinical Team Leader, DAAAP
Dan Mellon, PhD  Supervisory Pharmacologist, DAAAP
Prasad Peri, PhD  Branch Chief, Division III, Branch VIII, Office of New Drug Quality Assessment (ONDQA)
Julia Pinto, PhD  Pharmaceutical Assessment Lead, ONDQA
Yun Xu, PhD  Team Leader, Clinical Pharmacology, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP), Office of Translational Science (OTS)
Silvia Calderon, PhD  Team Leader, Controlled Substance Staff (CSS)
Robert Levin, MD  Clinical Reviewer, DAAAP
Elizabeth Bolan, PhD  Preclinical Pharmacology Reviewer, DAAAP
Arthur Shaw, PhD  Chemistry Reviewer, Division III, Branch VIII, ONDQA
John Duan, PhD  Biopharmaceutics Reviewer, ONDQA
Srikanth Nallani, PhD  Clinical Pharmacology Reviewer
James Tolliver, PhD  Pharmacologist, CSS
IND 075786
Meeting Minutes

Kim Lehrfeld, PharmD                      Team Leader, Division of Risk Management
(DRISK), Office of Medication Error Prevention and Risk
Management (OMEPRM), Office of Surveillance and
Epidemiology (OSE)

Jamie Wilkins Parker, PharmD TCon         Risk Management Analyst, DRISK, OMEPRM, OSE (via
TCon)

James Schlick, RPh, MBA                   Safety Evaluator, Division of Medication Error and
Prevention, OMEPRM, OSE

Tara L. Argual, PharmD LCDR, USPHS         Senior Safety Evaluator Division of
Pharmacovigilance 2 (DPVII); Office of Surveillance and
Epidemiology (OSE)

Lisa Basham, MS                           Senior Regulatory Health Project Manager, DAAAP

SPONSOR ATTENDEES
Michael Heffernan, RPh                    CEO and President
Ernest A. Kopecky, PhD, MBA               VP, Clinical Development
Alison Fleming, PhD                       VP, Product Development
Said Saim, PhD                           VP, Pharmaceutical Development
Steve Mayock, BS                          Director of Analytical Development and QC
Doug Carlson, BS                          VP, Corporate Development
Melinda O’Connor, BS                      Director, Clinical Operations (via telecon)
Ravi Varanasi, BS                        Associate Director, Product Development (via telecon)
(Pharmacokineticist)
(Statistical Consultant)
(Statistical Consulting)
(NDA Submission Support) (via TCon)

BACKGROUND

Oxycodone DETERx is a novel abuse-deterrent formulation with the proposed indication of
management of pain severe enough to require daily, around-the-clock, long-term opioid
treatment and for which alternative treatment options are inadequate. The dosage form is an
extended-release capsule with an oral dosing regimen of every 12 hours. The proposed strengths
are 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg. A Pre-IND meeting was held on March 8, 2007,
and the IND was granted Fast Track Designation on December 12, 2007. An End-of-Phase 2
meeting was held on March 30, 2010. The Sponsor submitted a Pre-NDA meeting request on
January 28, 2014, with the purpose of discussing the NDA submission requirements for
Oxycodone DETERx. The meeting package arrived on March 4, 2014. The proposed 505(b)(2)
reference is OxyContin. Preliminary responses were emailed to the Sponsor on April 10, 2014.
On April 15, 2014, the Sponsor indicated via email that they wish to discuss our responses to
Questions 3(a), 3(b), 5(a) (if time permits), 5(b), Additional CSS Comments under 6, 7, 10, 13,
14, 18, and 19(a). The Sponsor emailed slides (“Meeting Exhibit Materials”) to facilitate
discussion on the evening of April 15, 2014 (attached).

DISCUSSION

For reference, your questions are reproduced below in italicized text. Our responses follow in
bold text. Discussion during the meeting is labeled as such and follows in normal text.
Discussion during the meeting is labeled as such and is in normal text.

Clinical Studies in Support of 505(b)(2) Strategy

Question 1
Consistent with advice obtained during the End-of-Phase 2 meeting (EOP2 meeting minutes
dated 04/29/2010, Question 3a), Collegium intends to file a 505(b)(2) NDA utilizing OxyContin
OP (NDA #22-272) as the reference product with the following studies supporting the bridge:

• CP-OXYDET-15 (Single-dose PK and food effect versus OxyContin OP),

• CP-OXYDET-18 (Multiple-dose PK and food effect versus OxyContin OP),

• CP-OXYDET-08 (12-week safety, tolerability, and efficacy in patients with chronic low back
pain, conducted to provide additional substantial evidence of the safety, tolerability, and
effectiveness of Oxycodone DETERx).

Details on the study designs and objectives are provided in Section 10.2 of the briefing package.
Collegium believes that these studies will provide the evidence needed to support the approval of
this product for the management of pain severe enough to require daily, around-the-clock,
longterm opioid treatment and for which alternative treatment options are inadequate,
understanding that the final determination is a review issue. Does the FDA agree?

Agency Response:
• See the section titled “505(b)(2) Regulatory Pathway” at the end of this document.
  We agree with your overall bridging strategy and with the study design of CP-
  OXYDET-08.

• In addition, provide published literature or in-house data to address the need for
dose adjustments based on age, gender, hepatic impairment, and renal impairment.

• Address the dose-proportionality of different strengths of your product based on the
  advice given in response to Question 6 at the EOP2 meeting.

DISCUSSION: No discussion necessary.
**Question 2**

Collegium submitted Serial Submission 0060 to IND 75,786 on 07/24/13, which contained our revised statistical analysis plan (SAP), mock-ups of key tables, proposal for handling of missing data in chronic pain studies, and responses to the Agency’s 08/30/12 questions pertaining to handling of missing data methodology for Study CP-OXYDET-08. The SAP has been reproduced as Appendix A to this briefing package for ease of reference. The Agency provided Collegium with a response letter dated October 8, 2013.

a. **In response to Question 3**, the Agency stated “Your proposed methodology is acceptable. However, you should also conduct an additional sensitivity analysis where subjects that discontinue due to other reasons are treated as those that discontinue due to adverse events.” Collegium understands and agrees with the importance of sensitivity analyses. As indicated in the SAP (Appendix A), we are planning to address the possibility of a low pain score being attributed to patients who drop out due to poor clinical outcome such as an adverse event (AE). Because the methodology for the analysis of the primary endpoint requires sub-setting the overall population based on reason for study discontinuation, we have instituted a blinded, ongoing, review process that evaluates each subject who discontinues the study prematurely to ensure that the reason for study discontinuation is correctly captured. A key component of this review process is to ensure that AE discontinuations are not incorrectly categorized as some ‘Other’ reason for discontinuation; the comment associated with the reason for discontinuation will be considered in the disposition. Given the efforts to minimize (or eliminate) any adverse discontinuations categorized as ‘Other’ discontinuations, we believe that an additional sensitivity analysis that treats ‘Other’ discontinuations as if they might be an AE discontinuation would erroneously bias the overall study results. Based on this rationale, Collegium does not intend to include a sensitivity analysis where subjects who discontinue due to ‘Other’ reasons are treated as those who discontinue due to AEs. Does the Agency agree?

**Agency Response:**

We note your response and appreciate that you will carefully adjudicate the reason for any discontinuation. However, if there are a large number of discontinued subjects classified as “other,” we will conduct additional analyses where discontinued subjects are treated as discontinued due to adverse events.

**DISCUSSION:** No discussion necessary.

b. **In response to Question 4a**, the Agency stated “While the proposed SAP is acceptable, an additional analysis to consider is a multiple imputation approach where imputation is based on the reason for discontinuation, ensuring that subjects that discontinue due to AE’s receive a bad clinical outcome.”

As noted in Section 8.1.1 of the SAP (Appendix A), the primary endpoint analysis accounts for the reason for discontinuation in the statistical model. Specifically, Section 8.1.1 of the SAP proposes the use of a finite mixture model where membership in the
components of the finite mixture is defined by reason for study discontinuation. Use of the finite mixture model was motivated by two considerations:

- The response trajectories of the subset of subjects who complete the study are likely to be substantially different from the response trajectories of the subset of subjects who discontinue the study due to lack of efficacy. The finite mixture approach allows for the incorporation of these differences in response into the overall model.

- Sub-setting the model based on the reason for discontinuation provides a realistic scenario regarding pain management for subjects who must discontinue treatment due to an AE. Section 8.1.4.2 of the SAP describes a sensitivity analysis in which the subset of subjects who discontinue the study due to AE are given increasingly poor responses. The impact of ensuring that these subjects have poor responses on the overall study results is summarized graphically.

Based on these considerations, we feel that the issues said to be addressed by the additional multiple imputation analysis (sub-setting based on reason for discontinuation, assigning poor responses to subjects who discontinue due to AEs) are addressed with the analyses defined in the SAP. Does the Agency agree?

Agency Response:  
Yes, our previous comment was only a recommendation for an additional analysis, not a requirement.

DISCUSSION: No discussion necessary.

Pre-Marketing Assessment of Abuse-Deterrent Properties

Question 3
Collegium has conducted laboratory-based in vitro manipulation and extraction studies (“Category 1”) on Oxycodone DETERx and appropriate comparator products consistent with the January 2013 Draft Guidance for Industry, “Abuse-Deterrent Opioids – Evaluation and Labeling”. A table outlining these “Category 1” studies is provided in the briefing package (Table 4).

a. Does the Agency agree that the studies outlined are a complete in vitro assessment of the abuse-deterrent properties of the formulation? If not, what studies should be added?

Agency Response:  
No. You have not provided complete protocols for the in vitro physical manipulation and chemical extraction studies. Overall, the types of studies being listed (physical manipulation, solvent extraction studies, multi-step isolation studies, intravenous studies, and vaporization studies) appear reasonable. However, the extent to which each of these
studies is complete and scientifically rigorous cannot be determined in the absence of complete protocols describing the methods to be used. Note the comments provided below regarding in vitro studies.

1. All in vitro studies submitted in support of the NDA should be conducted on the to-be-marketed formulation.

2. In vitro studies should be done by an outside, independent laboratory.

3. In extraction studies, extend the duration of extraction long enough to result in a range of less that 20% to greater than 80% of extraction of oxycodone per label claim.

4. In the small volume extractions for intravenous injection, evaluate both intact and crushed microspheres using water (5 and 10 mL) maintained at room temperature and preheated and maintained at 90º-95º C, but not boiling. Extraction times should range from 0.5 seconds to 30 minutes. In addition to determining the amount of oxycodone extracted, the volume and viscosity of the solution should be determined. In addition, evaluate syringeability using 5 and 10 mL of water.

5. Since the microspheres containing oxycodone base have increased solubility at lower pH, evaluate the extraction of oxycodone using water adjusted to a lower pH in the range of 4 to 5.5. In addition, evaluate the extraction of oxycodone using ethanol/water as a solvent.

6. Specify the dissolution conditions in your protocol. Conduct the dissolution studies under different pH conditions and rotation speeds.

DISCUSSION:
Regarding the Agency’s response in Number 2 above the Sponsor stated that all of their in vitro abuse-deterrence studies were performed in their internal GMP laboratory. A subset of the abuse-deterrence studies was sent to an independent lab, which verified the results. The Sponsor asked if future studies could be performed in their internal laboratory. The Agency encouraged the Sponsor to conduct new studies in an independent laboratory, but stated that in-house studies with a subset sent to an independent lab for verification was an acceptable approach.

Referencing the Agency’s response Number 3 above, the Sponsor asked whether monitoring extraction for a maximum of 24 hours is sufficient with solvents and conditions that result in less than 80% extraction in 24 hours, e.g., olive oil, in which only about 20% extraction is observed in 24 hours. The Agency agreed that 24 hours is sufficient for those conditions.

Referencing the Agency’s response Number 4 above, the Sponsor questioned whether the specified time point of 0.5 seconds is an error. The Agency confirmed that the response was intended to read 0.5 minutes.
Regarding the Agency’s response to Number 6 above, the Agency requested more detail about how the extraction studies on pages 18 and 19 of the Meeting Exhibit Materials provided by the Sponsor were conducted, specifically, whether the studies in which the product was pre-soaked in solvents and then placed into dissolution media for measurement of drug release were conducted in addition to or in lieu of the standard in vitro extraction studies where drug is placed directly into solvents of different pH and measured directly in the solvent. The Sponsor clarified that the soaking studies using the QC dissolution method as an endpoint were conducted in addition to the required standard extraction studies. The Agency stated that, because the pre-soaking studies were performed in addition to the extraction studies, assuming the extraction studies meet the requirements, the pre-soaking studies using the QC dissolution method as an endpoint should be acceptable and it is not necessary to explore additional pH and rotation speeds for that study set.

b. Collegium has conducted the majority of the in vitro manipulation and extraction studies within its own analytical laboratory. The studies were scientifically rigorous, conducted under protocol, and the data subjected to a review process. A subset of the studies regarding the effect of physical manipulation was confirmed by an independent laboratory: Collegium does not intend to repeat the full complement of studies in a third party laboratory. Does the Division agree with this approach?

Agency Response:
Yes, confirmation of the results of a subset of the studies regarding the effect of physical manipulation by an independent laboratory is acceptable for this application. However, we prefer that Sponsors have outside, independent laboratories conduct in vitro manipulation and extraction studies on products under development. For any future product development, you are encouraged to have all in vitro manipulation and chemical extraction studies conducted by outside, independent laboratories.

DISCUSSION: See discussion under 3(a), above.

c. Collegium proposes that these studies will be summarized in Module 2.3 (Quality Overall Summary) and the detailed design and results will be provided in Module 3.2.P.2.2.3 (Physiochemical and Biological Properties). Appropriate cross references will also be provided in sections of the NDA where in vitro manipulation and extraction data are relevant. Does the Agency agree with this approach?

Agency Response:
Yes. This is acceptable.

DISCUSSION: No discussion necessary.

d. Consistent with advice obtained from the Agency for a product utilizing the DETERx technology with a different active (Oxymorphone DETERx, IND 106,830, pre-IND
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Does the Agency agree with this approach?

Agency Response:
Yes. This is acceptable.

DISCUSSION: No discussion necessary.

Question 4
Collegium is conducting a clinical program ("Category 2" and "Category 3" studies) to evaluate the abuse-deterrent properties of Oxycodeone DETERx. A description of the studies (CP-OXYDET-17, CP-OXYDET-19, CP-OXYDET-21, CP-OXYDET-24, and CP-OXYDET-25) is presented in Section 10.3.2 of the briefing package. Does the Agency agree that the completed and planned studies provide an adequate Category 2 and Category 3 assessment of the abuse-deterrent properties of Oxycodeone DETERx to support Tier 2 and Tier 3 labeling?

Agency Response:
The completed and ongoing studies appear to have the potential for providing some level of understanding about the abuse potential of Oxycodeone DETERx. Ultimately, assessment of proposed claims must await complete review of all data submitted under an NDA.

Also see responses to Questions 5 a & b.

DISCUSSION: No discussion necessary.

Question 5
The clinical program outlined in the briefing package includes several studies where PK data comparing manipulated and intact dosage forms were collected for the oral route of administration. Specifically:

- CP-OXYDET-17 evaluated the PK profile of Oxycodeone DETERx following both physical manipulation and chewing relative to intact oral administration in both the fed and fasted states and to an IR comparator in the fasted state;
- CP-OXYDET-24 will evaluate the PK profile and subjective drug effects, comparing chewed Oxycodeone DETERx to intact administration in both the fed and fasted states and to crushed IR tablets in the fasted state; and
- CP-OXYDET-25 will evaluate the PK profile of Oxycodeone DETERx and OxyContin OP, both following physical manipulation and intact oral administration, relative to crushed IR tablets in the fed state.

The findings of Study CP-OXYDET-17 are summarized in Section 10.3.2.1 of the briefing package.
a. Consistent with advice obtained from FDA in the EOP2 meeting (EOP2 meeting minutes dated 04/29/2010, Question 9a), Collegium proposes to include Study CP-OXYDET-17 data in the Pharmacokinetics section of the product label (Section 12.3) in order to illustrate the lack of impact of chewing and physical manipulation (i.e., crushing) on the PK profile. Does the Division agree with this approach?

Agency Response:
As advised in December 2013, conducting an oral human abuse potential study would place the pharmacokinetic results from study CP-OXYDET-17 into the proper perspective for evaluating the possible abuse-deterrent properties of the DETERx formulation when administered orally, crushed or chewed, compared to intact product. Based on the study results from study CP-OXYDET-17, conduct an oral human abuse potential study to evaluate the effect of food on drug liking, and to address the effect of manipulation under fasted conditions. This abuse potential study should consist of at least four arms including intact capsules under fed (High Fat High Calorie meal, HFHC) and fasted conditions, chewed capsules under fasted conditions, and a placebo. We note that the design of study CP-OXYDET-24 is consistent with this advice, as provided in the letter dated December 3, 2013. Ultimately, assessment of specific claims must await complete review of all data submitted under an NDA.

DISCUSSION: Time did not permit discussion of this response.

b. Based on the PK data from studies (CP-OXYDET-17, CP-OXYDET-24, and CP-OXYDET-25) in conjunction with the in vitro data outlined in the briefing package in Section 10.3.4, and consistent with label instructions that the capsule may be opened for sprinkle administration, Does the Division agree with this approach?

Agency Response:
See response to Question 7 with regard to labeling your product for use as sprinkles for oral administration.

DISCUSSION:
Slides 3-6 of the Meeting Exhibit Materials pertain to this discussion. The Sponsor cited the Agency’s April 23, 2013, Advice letter wherein the Agency agreed that “…the mortar and pestle alone, in contrast to the use of less effective methods of manipulation, would be sufficient for the in vivo pharmacokinetic study.” They shared slide Number 3 of the Meeting Exhibit Materials,
showing the lower particle size and higher release from material manipulated using the mortar and pestle, compared with material from other manipulation methods. The Agency noted that the same letter stated that “the mortar and pestle should not be taken as a substitute for manipulation by chewing.” The Sponsor summarized the results of two studies (CP-OXYDET-17 and CP-OXYDET-25) demonstrating that neither chewing nor crushing alter the PK profile of the pellets in Oxycodone DETERx. The Agency requested an explanation for the difference in technique used in the studies to administer drug, i.e., crushing the pellets, placing the material into a vial, having subjects place the material into their mouths, and then follow with water, in contrast to the IR oxycodone, which was in solution when ingested. The Sponsor stated that the wax beads, even when crushed, will not dissolve and will not go into suspension, even with continuous stirring. Rather, they float and stick to the sides of the vessel. They added that this is the reason that they performed the soaking studies, i.e., to see if the different solvents changed the integrity of the beads. Their goal was to identify the primary method people might abuse the drug and study all other parameters under those conditions. The Agency confirmed that the mortar and pestle is the most effective means of physical manipulation, that use of the mortar and pestle alone would be sufficient for the in vivo PK study, and that no further studies using less effective manipulation methods would be required. The Division noted that cutting and breaking studies are not applicable to capsule formulations.

Question 6
The clinical program outlined in the briefing package includes two “Category 3” studies (CPOXYDET- 21 and CP-OXYDET-24).

- **Study CP-OXYDET-21** evaluated the abuse potential of intranasal administration of crushed Oxycodone DETERx relative to intranasal administration of a crushed oxycodone IR comparator and to oral administration of intact Oxycodone DETERx capsules.

- **Study CP-OXYDET-24** will evaluate the relative abuse potential of oral administration of Oxycodone DETERx (intact capsules administered fasted and fed), Oxycodone DETERx (chewed capsule contents administered fasted and fed), and crushed IR oxycodone tablets (administered fasted).

The study designs are consistent with the January 2013 Draft Guidance for Industry, “Abuse-Deterrent Opioids – Evaluation and Labeling”; moreover, Study CP-OXYDET-24 is consistent with specific FDA advice to Collegium (Advice Letter dated 12/03/13). The study designs for both studies and results for CP-OXYDET-21 are summarized in the briefing package in Section 10.3.2.

1. **CP-OXYDET-21** study results demonstrated a statistically significant reduction in likeability of crushed Oxycodone DETERx when compared with IR oxycodone with respect to the nasal route of administration based on the primary measure of peak “drug liking” (Emax). Additionally, the study results demonstrated a statistically significant reduction in likeability of crushed Oxycodone DETERx administered intranasally when compared with intact oral administration of Oxycodone DETERx capsules. Consistent
with the 2013 Draft Guidance for Industry, “Abuse-Deterrent Opioids – Evaluation and Labeling,” and with approved labeling for OxyContin, Collegium intends to include Study CP-OXYDET-21 data in the Drug Abuse and Dependence section of the product label (Section 9). Does the Division agree with this approach?

Agency Response:
It is possible that the results from study CP-OXYDET-21 may be suitable for inclusion in the Drug Abuse and Dependence section of Section 9 of the product label. However, whether this is done, and what specific results are included, will be determined following review of the NDA.

DISCUSSION: No discussion necessary.

b. It is anticipated that Study CP-OXYDET-24 will demonstrate reduced likability for chewed Oxycodone DETERx relative to crushed IR oxycodone with respect to the oral route of administration. Assuming the data support this finding, Collegium intends to include these study results in the Drug Abuse and Dependence section of the product label (Section 9). Does the Division agree with this approach?

Agency Response:
See prior response.

DISCUSSION: No discussion necessary.

c. Based upon the results of study CP-OXYDET-17, where it was demonstrated that crushing or chewing Oxycodone DETERx prior to oral administration did not result in enhanced plasma exposure to oxycodone (based on Cmax and AUC) relative to intact administration under fed conditions, it is anticipated that Study CP-OXYDET-24 results will demonstrate that there is no significant enhancement in the likeability of chewed Oxycodone DETERx relative to intact, fed administration of Oxycodone DETERx. Assuming the data support this finding, Collegium intends to include these study results in the Drug Abuse and Dependence section of the product label (Section 9). Does the Division agree with this approach?

Agency Response:
See prior response.

DISCUSSION: No discussion necessary.

Additional CSS Comments:
1. All information pertaining to the abuse potential assessment should be available in the NDA as specified in the draft guidance for industry, Assessment of Abuse Potential of Drugs, available at

Reference ID: 3508532
2. Summarize all cases from Phase 3 clinical study reports of actual or suspected abuse, misuse, noncompliance, and diversion in tabular form with narratives. Clearly state the criteria used to identify each of these cases. Submit the case report forms providing complete information on instances of abuse, misuse, noncompliance, and diversion in the NDA with a clear heading in the table of contents and appropriate links in the text. Consider providing an electronic link between the summary table and the case report forms. Refer to the draft guidance for industry, *Assessment of Abuse Potential of Drugs*, available at [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf).

3. Include adverse events and safety profiles pertinent to abuse potential and collected from Phase 1 and Phase 3 studies in the Integrated Summary of Safety. The primary focus should be on those studies utilizing the to-be-marketed formulation and not on studies of early formulations. Provide a table indicating the study design, population studied, doses, and routes of administration for each study, and a link to the adverse events summary.

**DISCUSSION:**
Pertaining to Item 3 above, the Sponsor shared their plan to summarize the adverse event data from Phase 1 studies in the ISS on a study-by-study basis rather than pool these data with the Phase 3 data for analysis because of the different subject populations. Phase 1 studies were conducted with naltrexone-blocked healthy volunteers or recreational drug abusers whereas the Phase 3 study was conducted with patients with chronic lower back pain. The Agency confirmed that this is acceptable.

**Alternative Dosage Administration**

**Question 7**

*In the FDA minutes recorded from the EOP2 Meeting, the Agency provided the following advice to Collegium: “If there are adequate PK data to support the safety of administering Oxycodone DETERx after the capsule has been manipulated, labeling for alternate methods of administration may be suitable.”* (EOP2 meeting minutes dated 04/29/2010, Question 9b)

Collegium intends to pursue labeling for alternate methods of administration of Oxycodone DETERx capsules (i.e. open capsule and sprinkle directly into mouth, sprinkle onto soft foods, or deliver through an enteral feeding tube). The strategy to support such labeling, which is consistent with previous advice from the Agency, is included in the briefing package. **Does the Division agree with the strategy to support such labeling?**
Agency response:
Labeling for alternate methods of administration may be acceptable based on adequate PK data from appropriate studies. You have provided a plan for an indirect comparison of data from Study CP-OXYDET-17 and in vitro studies. This type of indirect comparison or extrapolation is unconventional and is unlikely to support labeling. Provide support for why the bioavailability of your product consumed as sprinkles over applesauce/soft-food can be considered similar to the bioavailability following chewing or crushing, particularly under fasted or fed conditions (CP-OXYDET-17). Provide support for why the bioavailability of the intact product taken with a low-fat, low-calorie meal (one toast with decaf coffee) can be considered similar to the bioavailability following sprinkling of the contents of the capsule on soft foods (CP-OXYDET-15). Indicate if the final to-be-marketed formulations were used in these studies.

Note that a bioavailability study evaluating the PK of the drug product sprinkled over applesauce/soft food helps not only the labeling with regard to adult dosing, but also helps with pediatric dosing.

As indicated previously, evaluate the risk for adhesion of the capsule contents to enteral feeding tubes.

DISCUSSION:
Slides 7-9 of the Meeting Exhibit Materials pertain to this discussion. The Sponsor emphasized their interest in receiving labeling regarding alternate methods of administration. The Agency stated that the data generated thus far may be supportive of the proposed “sprinkle” language but could not guarantee that it will be adequate to support administration with soft food. The Agency also noted that the unconventional approach of utilizing data from an in vivo crushing study (CP-OXYDET-017) and an in vitro soft food dissolution study to support such a claim requires thorough review after NDA submission. If the Sponsor chooses not to conduct an additional in vivo study, the Agency will review the information, during the NDA review, to determine whether the available data from the different studies will meet the requirements to support labeling. The lack of an in vivo apple sauce/soft food study is not a filing or approvability issue. The Sponsor confirmed that all studies have been performed with the to-be-marketed formulation.

Content, Format and Submission of NDA

Question 8
Collegium intends to prepare the NDA for Oxycodone DETERx as an electronic submission structured according to eCTD requirements. Collegium’s subcontractor, [redacted], will submit the application. The Oxycodone DETERx submission will contain, per agreement (EOP2 meeting minutes dated 04/29/2010, Question 1a), one adequate and well-controlled study providing efficacy and safety data pertinent to the proposed indication. As such, Collegium intends to provide detailed summaries of clinical efficacy and safety in Modules 2.7.3 and 2.7.4, respectively. No separate integrated Summaries of Safety or Efficacy will be
prepared. Instead, Module 5.3.5.3 of the eCTD will include reference links to Modules 2.7.3 and 2.7.4 to enable a reviewer to easily find the summary efficacy and safety information. Does the Division agree with this approach?

Agency Response:
No. As a 505(b)(2) application, the ISE should include a discussion of how the findings from the single efficacy study, reliance on the Agency’s findings for the listed drug, and any cited literature references support a finding of efficacy for this product. The ISS should follow a similar approach and include a discussion of how the findings from the clinical studies, reliance on the Agency’s findings for the listed drug, and any cited literature references support a finding of safety for this product.

DISCUSSION: No discussion necessary.

Question 9
As noted elsewhere in this document, Collegium has conducted a series of Phase 1 PK and Pharmacodynamic (PD) studies in healthy volunteers, as well as the Phase 3 adequate and well-controlled safety, tolerability, and efficacy Study CP-OXYDET-08.

a. Collegium intends to submit all study data for Study CP-OXYDET-08 in SDTM/AdaM format. Does the Agency agree with this approach?

Agency Response:
Yes.

DISCUSSION: No discussion necessary.

b. As no integration with other data is required, coding for concomitant medications and adverse events will remain in the version that was used for the CP-OXYDET-08 study report. Does the Agency agree with this approach?

Agency Response:
Yes.

DISCUSSION: No discussion necessary.

c. Data from the Phase 1 studies will not be integrated with the data for Study CPOXYDET-08 for purposes of summarizing safety and efficacy for the following reasons:

- These studies enrolled healthy volunteers or drug-experienced abusers. This is a different population than that which was enrolled into Study CP-OXYDET-08 and
which will be the target population for Oxycodone DETERx should it be approved for marketing.

- Each of the healthy volunteer studies employed naltrexone blockade to minimize adverse effects from oxycodone exposure.

- The majority of the studies were Phase 1 in design and employed single doses of Oxycodone DETERx and/or comparators such as OxyContin or IR oxycodone (administered in various randomized periods in each study).

- None of the Phase 1 studies included any pain efficacy endpoints.

Does the Agency agree with this approach?

Agency Response:
Yes.

DISCUSSION: No discussion necessary.

d. For the single-dose Phase 1 studies, Collegium intends to create and submit a single analysis PK dataset that integrates the concentration data for oral administration of intact Oxycodone DETERx capsules and intact OxyContin tablets. The integration process will convert the PK concentration data into a uniform format across all Phase 1 studies. Collegium does not plan to submit any other datasets for the Phase 1 studies.

Does the Division agree with this approach?

Agency Response:
It is acceptable to submit a single analysis PK dataset that integrates the concentration data from different studies along with demographic data. However, submission of individual study datasets is still required.

DISCUSSION: No discussion necessary.

Non-clinical

Question 10
Collegium has conducted an analysis of the levels of inactive ingredients in the Oxycodone DETERx formulation based on the Maximum Theoretical Daily Dose (MTDD) provided by the FDA (EOP2 meeting minutes, Question 16) and has prepared a justification for the safety of these inactive ingredients based on available data in the literature. Per the advice of the Division during the End-of-Phase 2 meeting (EOP 2 meeting minutes, Question 11) Collegium has submitted this justification, along with copies of the literature references, to the IND for consideration (IND #75,786, Serial Submission 0048, 07/25/12). A copy of the justification
(without literature references) is included as Appendix C to the briefing package. While Collegium understands acceptance of this data is a review issue, does the Division have any comments on the content and format of the justification as submitted?

Agency Response:
Based on the information provided, several excipients in this drug product, when dosed up to the MTDD of oxycodone, are considered new excipients in that the doses via this drug product would result in higher daily doses than any other FDA approved drug product. Specifically, myristic acid, yellow beeswax, carnauba wax, and hypromellose are deemed new or novel excipients. Based on our initial review of the safety justification for myristic acid and hypromellose, you appear to have provided adequate rationale for their safety and the justification and references cited are suitable to file the NDA. However, based on the summary information provided in Appendix C of the meeting package, we have concerns about the adequacy of the safety justification for the beeswax and carnauba wax. Specifically, there appear to be limited actual toxicology data to support the safety of these two excipients, as recommended by the FDA guidance for industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf.

Although we are willing to review alternative safety justifications in lieu of actual toxicology studies, this approach does result in some risk to your development program, as we may not ultimately agree that adequate data exist to support the safety of the excipients when the product is dosed up to the MTDD of oxycodone. As you have acknowledged, a final determination of the adequacy of the safety assessment based on a detailed review of all of the data will be made during the NDA review cycle.

In order to complete this assessment during the NDA review, provide electronic copies of all of the articles cited in the safety assessment. In addition, reference to tertiary review articles containing only summary data are generally unacceptable as the primary data are not available for review. If review articles are used, provide copies of the original source material (i.e. primary references). In addition, describe how the endpoints assessed in the literature reports meet the standardized regulatory requirements of GLP toxicology studies. When data are not available, you must provide adequate justification as to why the missing data are not essential to support approval of your drug product. In the absence of adequate justification, additional studies may be required.

Based upon the preliminary review of the summary information provided, we are providing the following comments. These comments should not be deemed to be a complete list of concerns with the excipient data provided to date.

1. Although you have stated that the components of the waxes are poorly absorbed and the metabolites, if absorbed, are metabolized to compounds occurring endogenously, it is not clear how the exposure to these compounds compares to the levels found endogenously. If the levels that would occur after consumption of the MTDD exceed
the endogenous levels, further studies may be required to determine that there are no safety concerns for these excipients.

2. If you elect to justify the safety of the waxes based on the components of the waxes, specifically delineate what data exist for each component at the worse-case maximum daily dose via the drug product, list what data are missing, and provide adequate justification for why the lack of those missing data should not be deemed a deficiency for the NDA.

3. As the beeswax and carnauba wax we may evaluate the existing safety data for the mixture or components both independently for each excipient as well as combined for a total wax MTDD of mg per day.

4. Based on the dietary levels predicted for both waxes, the previous clinical experience is lacking to support safety at the MTDD.

5. Since both of the waxes are derived from natural products, your NDA must include information regarding the potential impurities in the wax derived from the environment. Of particular concern is the potential for residual Purity information should be provided either in the NDA or via reference to an acceptable master file for the excipient material.

6. Given the potential for significant wax accumulation in the gastrointestinal tract, we are concerned that there may be GI obstruction with the material with large doses of this drug product.

For any novel excipients, provide a DMF reference (with appropriate letter of authorization) or, alternatively, provide information in your NDA pertaining to the manufacture, control and of the excipient. Further, provide a certificate of analysis for each of the excipients in the drug product.

DISCUSSION:
The Sponsor stated their intention to review the literature and revise the safety justification to address the Agency’s concerns pertaining to dosing beeswax and carnauba wax at the MTDD for oxycodone. They will also address concerns about residual in Section 3 of the NDA. The Sponsor asked whether there is a mechanism to receive feedback on their safety justification prior to NDA submission. The Agency responded that pre-review of the preclinical section of the NDA will not be feasible but that guidance may be provided as resources permit. The Sponsor should not hold up NDA submission, however, in anticipation of receiving feedback. The Sponsor should leverage as much available information as possible to allow the Agency to make a clear determination of safety at the MTDD of oxycodone. The Agency emphasized that a concern with reference to literature articles on natural products is that it is unlikely that adequate data will be available to assure that the batches tested are
representative of the drug product excipients proposed for use. Lack of adequate data to show comparability may preclude extrapolating safety from published literature.

**Outstanding CMC Questions- Drug Substance**

**Question 11**
A table containing impurity specifications for drug substance, comparing the maximum daily exposure with ICH Q3A limits is provided in the briefing package. A justification for proposed impurity limits is also provided. Does the Division agree with the approach presented for the proposed limits for the drug substance?

**Agency Response:**
The specification for 7-methyl oxycodone in the drug substance exceeds the ICH Q3A(R2) threshold for qualification. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:

- You must conduct a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90 days should be completed.

**DISCUSSION:** No discussion necessary.

**Question 12**
As described and justified in the briefing package, and based on FDA’s recommendations in the End-of-Phase 2 meeting minutes, Collegium has revised its proposed NDA specifications relating to the drug substance. Does the Division agree with the overall approach for setting drug substance specifications?

**Agency Response:**
Acceptability of release and stability specifications is made during the review process and is dependent on the totality of the data submitted.

**DISCUSSION:** No discussion necessary.
**Outstanding CMC Questions- Drug Product**

**Question 13**
Oxycodone DETERx microspheres are manufactured using oxycodone base as the drug substance. The capsule strengths are 9.0 mg, 13.5 mg, mg, mg, mg, and mg oxycodone base. The December 2013 Guidance for Industry, “Naming of Drug Products Containing Salt Drug Substances”, stipulates that the drug product names should be established as determined under the USP Salt Policy in all contexts in which a product’s established name is used, but that CDER is applying exceptions.

**Agency Response:**
You may include labeling about the oxycodone hydrochloride equivalent in Section 2 Dosage and Administration to improve prescribers’ understanding of how to dose this product.

**DISCUSSION:**
The Division responded that, in accordance with the draft guidance for industry, Naming of Drug Products Containing Salt Drug Substances, available at [http://www.fda.gov/downloads/drugs/guidanceregulatoryinformation/guidances/ucm379753.pdf](http://www.fda.gov/downloads/drugs/guidanceregulatoryinformation/guidances/ucm379753.pdf), Oxycodone DETERx will be labeled as the base. The Agency stated that equivalency statements and cautions will be prominently included in the Prescribing Information and packaging to ensure that prescribers and pharmacists understand how the dose strengths relate to other marketed products. The Agency added that rounding the doses to whole numbers maybe a possibility and will be discussed internally during NDA review.

**Question 14**
A table containing impurity specifications for drug product, comparing the maximum daily exposure with ICH Q3B limits is provided in the briefing package. A justification for proposed impurity limits is also provided. Does the Division agree with the approach presented for the proposed limits for drug product?

**Agency Response:**
Acceptability of release and stability specifications is made during the review process and is dependent on the totality of the data submitted.
The specification threshold for qualification. See Question 11.

DISCUSSION:
The following discussion references Slide 11 in the Meeting Exhibit Materials. The Sponsor asked whether the Agency would support a proposed specification for the degradation product if it is supported by a published compendial limit for a scientifically justified reference product. The Agency stated that it follows the ICH and the regulations are clear. Support for the proposed limit must be justified based on one of the following: 1) evidence that the impurity is a major metabolite; 2) data that the proposed limit for the impurity is comparable, at either the beginning, middle, or end of the shelf life, to the impurity level observed in multiple batches of the 505(b)(2) referenced product; or 3) toxicological safety qualification data for the impurity. Alternatively the Sponsor has the option of revising the acceptance criteria to meet ICH recommendations.

Question 15
As described and justified in the briefing package, and based on FDA’s recommendations in the End-of-Phase 2 meeting minutes, Collegium has revised its proposed NDA specifications relating to the drug product. Does the Division agree with the overall approach for setting drug product specifications?

Agency Response:
You have not addressed the following concerns regarding your dissolution methodology that we raised in our advice letter dated April 23, 2013:

“…method is under-discriminating because, while the in vitro test demonstrates similarity, the in vivo study demonstrates a difference in exposure. We acknowledge, however, that the PK study was conducted under fed conditions, which makes the interpretation of these data inconclusive due to a possible confounding food effect. Therefore, submit additional data to further support the discriminating ability of the proposed dissolution method (e.g. if available, submit data showing that the method is able to reject batches that are not BE)."

Address these concerns before your next proposal for the dissolution specification.

DISCUSSION: No discussion necessary.

Question 16
Collegium intends to market a drug product protocol has been prepared (Appendix E) and will be submitted in the NDA which will include

Reference ID: 3508532
the planned studies and supporting data regarding the product performance, safety, and controls. Does the Division agree with the overall strategy proposed for the comparability protocol approach as outlined in the briefing package?

Agency Response:
Yes, your strategy seems reasonable. The data should be provided.

Include a dissolution profile comparison with f2 criterion (>50) in the proposed comparability protocol.

DISCUSSION: No discussion necessary.

Question 17
An outline of the ongoing stability program for the primary and supporting stability batches is included in the briefing package. At the time of filing, Collegium intends to provide a minimum of 18 months of long-term stability data, 12 months of intermediate stability data, and 6 months of accelerated stability data for the 3 primary stability batches. Additionally, 24 months of long-term stability data, 12 months of intermediate stability data, and 6 months of accelerated stability data will be submitted for a supporting batch manufactured at the same site, at the same scale, and using the same process as the primary stability lots. Does the Agency agree with the strategy regarding submission of stability data?

Agency Response:
The amount of stability data planned for submission seems reasonable.

DISCUSSION: No discussion necessary.

Biopharmaceutics

Question 18
A report containing alcohol interaction in vitro dissolution studies, conducted in dissolution media simulating the fed state and in dissolution media simulating the fasted state is provided as Appendix F to the briefing package. Does the Agency agree that the submitted data support a biowaiver for in vivo alcohol interactions studies?

Agency Response:
No, the comparisons you made between the dissolution profiles with and without alcohol were in different media (the dissolution with alcohol in 0.1 N HCl and the dissolution without alcohol in pH 4.5 medium, respectively). You should have made the comparisons in the same medium (0.1 N HCl).
When the dissolution profiles in 0.1 N HCl with and without alcohol were compared, dose dumping potential could not be excluded, especially for the lower strengths.

**DISCUSSION:**
This discussion references slides 13-15 of the Meeting Exhibit Materials. The Sponsor referenced an advice letter from the Agency in which the Agency agreed that the results in the Quality Control (QC) medium show no indication of dose dumping. The Agency acknowledged that agreement but noted that it was also stated that dissolution should be evaluated in 0.1N HCl. The Sponsor stated that, due to suppression of dissolution in 0.1N HCl, the appropriate baseline for assessment of dose dumping is the QC media. They presented Slide 14, which illustrates that release is blunted in 0.1N HCl media. The Sponsor asked whether, based on the data submitted, they must conduct an in vivo alcohol dose dumping study. The Agency reiterated that the potential for dose dumping in 0.1N HCl should be evaluated against the 0.1N HCl media without alcohol, regardless of the fact that dissolution is suppressed in this media. If, following the proper in vitro studies, there is evidence of dose dumping, the Sponsor must conduct an in vivo study to get a definitive answer about the risk for alcohol dose dumping. A reduced study design for the in vivo study with 40% alcohol, rather than a full study using 0%, 4%, 20% and 40% alcohol, may be sufficient if no dose dumping is observed. However, if there is evidence of dose dumping, then the full study will be required. The in vivo study should be performed with the highest and lowest strengths. The Agency stated that the study should be performed under fasted conditions and would be willing to review the protocol in an expedited fashion.

**Pediatric study Proposal**

**Question 19**
At the Collegium EOP2 meeting, Collegium sought agreement on its plan with respect to pediatric studies. The Agency provided the following response in the EOP2 official meeting minutes (dated 04/29/2010): “We agree with the waiver for ages birth to less than 2 years of age. However, there is no rationale at this time for deferring studies in children ages 2 to 17 years until after this product is approved in adults.”

In the EOP2 official meeting minutes Discussion, “The Sponsor requested confirmation that there is no requirement to study their drug in pediatrics prior to submission of the NDA. The Division explained that the Sponsor should start developing an age-appropriate formulation and study protocols, and provide an update as to the status at the time of NDA submission.”

a. Does the Agency agree that no additional actions are required prior to NDA submission?

**Agency Response:**
No. As per the draft guidance for industry, *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072114.pdf, you must submit your initial pediatric study plan (PSP) no later than 210 calendar days before the marketing application. We acknowledge that during the End-of-Phase 2 meeting on March 30, 2010, which occurred prior to the release of the guidance, we said that you should start developing an age-appropriate formulation and study protocols, and provide an update as to the status at the time of NDA submission. However, we believe that there was sufficient time from the date of publication of the guidance in July 2013 to have prepared a PSP. We expect your PSP within 60 days of your Pre-NDA meeting and no later than 210 days prior to submission of your NDA application. Applications submitted on or after January 15, 2014, without an agreed upon PSP are at risk of refusal to file.

DISCUSSION:
The Sponsor noted that the Pediatric Plan is under development. They intend to submit the iPSP on May 15, 2014. This would not be 210 days prior to NDA submission, which is planned for November of 2014. The Agency concurred with the proposed timeline.

b. Collegium is requesting a modification to the Agency’s prior agreement (EOP2 meeting) with Collegium to waive pediatric study requirements for ages birth to less than 2 years of age. Does the Agency agree with Collegium’s waiver request?

Agency Response:
Yes.

DISCUSSION: No discussion necessary.

c. To satisfy the Pediatric Research Equity Act (PREA) requirement for pediatric studies, Collegium intends to conduct two pediatric studies after NDA approval. Does the Agency agree with these pediatric studies?

Agency Response:
Yes, we agree with the general approach as outlined above.

DISCUSSION: No discussion necessary.
d. In July 2013, the Agency released draft Guidance for Industry entitled “Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans” that stipulates the conditions under which a Pediatric Study Plan is required and the timing for that submission. Collegium’s EOP2 meeting was conducted before the issuance of this draft guidance; Collegium’s Phase 3 study was also started before issuance of this draft guidance. Collegium intends to continue to proceed according to the current plan and does not plan to submit a Pediatric Study Plan 210 days before the marketing application is submitted. Does the Agency agree with this approach?

Agency Response: No. Refer to the response to question 19a.

DISCUSSION: No discussion necessary.

Question 20
In July of 2012, FDA released a set of template Risk Evaluation and Mitigation Strategy (REMS) documents intended be generally applicable to the REMS programs developed for each member of the extended-release/long-acting opioid therapeutic class. For purposes of the present NDA, Collegium intends to develop a REMS based on the classwide documents prepared by FDA in consultation with Industry. Some sections of these documents will be modified to render them more product-specific for Oxycodeone DETERx. Other classwide sections will also be modified to reflect the fact that certain elements of the REMS and associated plans have been formally implemented since the initial release of these documents. Does the Division agree with this approach?

Agency Response: If you are in the process of joining the REMS Program Companies (RPC), if approved, this application will have a slightly modified ER/LA REMS which incorporates your product specific information. It is our hope that you will be a full member at the time of your NDA submission and that the RPC will provide the most recently approved ER/LA REMS documents for you to revise. However, if you are still in the process of joining at that time, base your revised REMS documents on the most recently approved ER/LA REMS materials on the FDA REMS website.

DISCUSSION: No discussion necessary.

Question 21
In Section 1.2., Elements to Assure Safe Use, of the classwide REMS for extended-release and long-acting opioid analgesics that Collegium intends to develop, Collegium does not intend to reproduce the ER and LA opioid REMS website (www.ER-LA-opioidREMS.com) content in the
**Oxycodone DETERx REMS document.** Due to the dynamic nature of the content of the ER-LA REMS website, Collegium instead intends to reference the REMS website by providing the URL in the Oxycodone DETERx REMS document. Does the Agency agree with this approach?

**Agency Response:**
We understand the dynamic nature of a website, however, the ER/LA REMS website is a component of the REMS, and thus must be included in a complete REMS submission. Therefore, you must include the website with your submission.

**DISCUSSION:** No discussion necessary.

**Question 22**
Oxycodone DETERx was previously designated as a Fast Track Development Program. The January 2013 Draft Guidance for Industry, “Abuse-Deterrent Opioids- Evaluation and Labeling,” states, “FDA considers the development of [opioids formulated to deter abuse] a high public health priority”. Collegium believes this product should be considered for priority review by the Division once the NDA is submitted. A brief summary of Collegium’s justification for priority review status is provided in Section 10.11.3 of the briefing document. Collegium intends to formally request a priority review at the time of filing the NDA. Does the Division agree with this approach?

**Agency Response:**
At the time of filing, you may request a priority review and we will review your request package. The best way to assure priority review would be to demonstrate improvement in the abuse deterrence properties of Oxycodone DETERx compared to a marketed formulation. Head-to-head data showing the potential for abuse deterrence is required and not simply a discussion of why abuse deterrence must be a high public health priority.

**DISCUSSION:** No discussion necessary.

**Additional Comment:**
We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the guidance for industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

**DISCUSSION:** No discussion necessary.
KEY DISCUSSION POINTS:

1. The Agency prefers and recommends that in vitro abuse-deterrence studies be performed by an independent laboratory but will accept data from the Sponsor’s internal laboratory.

2. For in vitro extraction studies, twenty-four hours is sufficient for monitoring extraction in solvents and conditions where less than 80% is extracted in 24 hours. When solvents and other extraction conditions (i.e., elevated temperature) allow for full extraction, the time points for analysis should be selected to clearly delineate the time course of extraction from less than 20% to greater than 80% extraction, including when the extraction curve reaches a plateau.

3. In our response to Question 3a, our item 4 should have read, “Extraction times should range from 0.5 minutes to 30 minutes.”

4. Cutting and breaking studies are not relevant for a capsule formulation. Mortar and pestle adequately covers the crushing methodology for the in vivo PK study. No further studies using less effective manipulation methods are required.

5. Adverse events for Phase 1 and Phase 3 studies need not be pooled in the ISS.

6. The Sponsor is interested in pursuing labeling for alternate methods of administration, namely, sprinkling the contents onto food. The completed studies are sufficient for NDA filing but labeling will be a review issue. A bioavailability study evaluating the PK of the drug product sprinkled over applesauce/soft food is the usual and most direct route to supporting this type of labeling.

7. The Sponsor may submit, prior to NDA submission, their support for the safety of the excipients in the drug product but the Agency cannot guarantee a full assessment prior to NDA submission.

8. The labeling will express the dose strength in terms of oxycodone base and the Agency will consider the possibility of rounding the doses to whole mg amounts. The label will include cautions and equivalency statements to avoid dosing errors.

9. The specification must not exceed the ICH Q3B(R2) threshold for qualification. If the specification exceeds this limit, a justification must be made and based on either 1) evidence that the impurity is a significant metabolite, 2) data demonstrating that the proposed limit is within the levels observed in the reference listed drug, or 3) qualification data for the impurity.

10. The Sponsor should conduct an in vivo alcohol interaction study. A reduced study design may be adequate.

11. The Sponsor plans to submit the PSP by May 15, 2014, and the NDA in November of 2014. This timeline is acceptable.
**PREA REQUIREMENTS**

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) 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. The PSP should be submitted in PDF and Word format.


**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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Corresponding names and titles of onsite contact:

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<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
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**505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at [http://www.regulations.gov](http://www.regulations.gov)).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any
published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

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<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
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<tr>
<td>1. Example: Published literature</td>
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<tr>
<td>2. Example: NDA XXXXXX “TRADENAME”</td>
<td>Previous finding of effectiveness for indication X</td>
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<td>3. Example: NDA YYYYY “TRADENAME”</td>
<td>Previous finding of safety for Carcinogenicity, labeling section XXX</td>
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Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.
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
05/16/2014
Dear Mr. Tan:

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

We also refer to the meeting between representatives of your firm and the FDA on March 30, 2010. The purpose of the meeting was to discuss your development plan and planned New Drug Application (NDA) submission.

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

If you have any questions, please call me at 301-796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes
MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 30, 2010

TIME: 10:30 – 11:30 AM (EST)

LOCATION: Food and Drug Administration
White Oak 22, Room 1309
10993 New Hampshire Ave
Silver Spring, MD 20993

APPLICATION: IND 075786

PRODUCT: Oxycodone DETERx

INDICATION: Chronic pain

SPONSOR: Collegium Pharmaceutical, Inc.

TYPE OF MEETING: End-of-Phase 2, Type B

MEETING CHAIR: Rob Shibuya, MD, Clinical Team Leader, Division of Anesthesia and Analgesia Products (DAAP)

MEETING RECORDER: Kathleen Davies, MS, Regulatory Health Project Manager

<table>
<thead>
<tr>
<th>FDA Attendees</th>
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<tbody>
<tr>
<td>Bob A. Rappaport, MD</td>
<td>Director, Division of Anesthesia and Analgesia Products</td>
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<tr>
<td>Sharon Hertz, MD</td>
<td>Deputy Director</td>
</tr>
<tr>
<td>Rob Shibuya, MD</td>
<td>Clinical Team Leader</td>
</tr>
<tr>
<td>Danae Christodoulou, PhD</td>
<td>CMC Lead, Office of New Drug Quality Assessment (ONDQA)</td>
</tr>
<tr>
<td>Sheldon Markofsky, PhD</td>
<td>Chemistry Reviewer, ONDQA</td>
</tr>
<tr>
<td>Robert Mello, PhD</td>
<td>Senior Microbiology Reviewer, New Drug Microbiology Staff, Office of Pharmaceutical Science</td>
</tr>
<tr>
<td>Patrick Marroum, PhD</td>
<td>Biopharmaceutics, ONDQA</td>
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<tr>
<td>Dan Mellon, PhD</td>
<td>Pharmacology Toxicology Supervisor</td>
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<tr>
<td>Beth Bolan, PhD</td>
<td>Pharmacology Toxicology Reviewer</td>
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<tr>
<td>Dionne Price, PhD</td>
<td>Statistical Team Leader</td>
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<tr>
<td>Jon Norton, PhD</td>
<td>Statistical Reviewer</td>
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<tr>
<td>Suresh Doddapaneni, PhD</td>
<td>Clinical Pharmacology Team Leader</td>
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<tr>
<td>Srikauth Nallani, PhD</td>
<td>Clinical Pharmacology Reviewer</td>
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<tr>
<td>Kathleen Davies, MS</td>
<td>Regulatory Health Project Manager</td>
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BACKGROUND

Collegium submitted an End-of-Phase 2 meeting request for guidance regarding their planned development program. Collegium would like to discuss their formulation and studies completed to date, their current development program, and identify any additional information necessary for an NDA submission under a 505(b)(2) regulatory pathway.

Each of the Sponsor’s questions is presented below in italics, followed by the Division’s response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on March 29, 2010.

CLINICAL

Question 1a. Collegium plans to complete additional pharmacokinetic studies (as outlined in Question 3) to comply with guidance provided in the PIND meeting, but does not intend to conduct any clinical studies to assess efficacy. Does the Agency agree with this approach?

FDA Response:
We do not agree with this approach. We refer to our previous comments regarding the pharmacokinetics of Oxycodeone DETERX. The studies you have reported do not allay our concerns about the potential for inconsistent therapeutic effect and potential for overdose given the large food effect of your product. Because of this, you will be required to conduct studies to characterize the safety and efficacy of your product under the proposed conditions of use.

You are proposing to establish the bioequivalence of your product to OxyContin (your proposed reference drug) under fed conditions and use these data along with other supportive pharmacokinetic data as a basis for approval for your product. To use a bioequivalence approach for approval, the proposed product must be bioequivalent to the reference product under fasting conditions. Your product is not bioequivalent to OxyContin under fasting conditions; it has substantially lower exposure.

After further consideration, since your product is not bioequivalent to the reference product and only comparable in the fed state, at least one adequate and well-
controlled trial of 12-weeks duration will be required to assess efficacy. We are concerned that efficacy will vary as a result of the effect that differences in meal composition will have on the pharmacokinetics of your product. Your study must include a method for carefully collecting data regarding meal size and composition, and subsequent efficacy.

Discussion:
Dr. Hertz initiated the meeting by stating that the Division is struggling with how evaluate the food effect associated with this product. In the fasted state, this product is not bioequivalent (BE) to OxyContin, the proposed reference drug. However, the product has similar pharmacokinetics (PK) to the reference drug in the fed state. Other currently approved products have a food effect; however, their food effect is not as large as this product. Thus, it is a challenge to predict the impact of the food effect with this product since it is not what is expected for opioids.

The Sponsor acknowledged this information and stated their intent is to proceed with this tamper-resistant product despite its food effect. The Sponsor explained that the product requires bile acid to release the oxycodone drug substance. Thus, their proposal is that the amount of food is irrelevant so long as food is consumed and they feel the product can be labeled accordingly without concern for safety issues.

The Sponsor further questioned how to alleviate the Division’s concerns about a food effect and what meaningful information would be generated from meal consumption data versus just noting whether a subject took their drug with or without food. The Sponsor asserted that they anticipate substantial difficulties if the Division requires that exact meal composition data are to be collected in Phase 3. The Division acknowledged the challenge of collecting such detailed data to address the food effect but noted that the issue must still be addressed.

The Division agreed that, if the Sponsor conducted a food effect study in which they measured the food effect at a minimum range of approximately 100 calories for a meal and found a similar food effect to a high fat meal, the Division would accept the collection of binary (“yes” or “no”) data to inform to whether a subject took their drug with food during subsequent studies instead of detailed meal composition data. It is important to know that all applicable food scenarios are addressed for this product, including at the low end of the caloric range, such that it can be concluded that “any” food consumption stimulates absorption. The Sponsor stated they would submit a food effect study to the IND for consideration by the Division.

The Sponsor also stated that they intend to resubmit their Special Protocol Assessment (SPA).

**Question 1b.** Collegium does not intend to conduct any additional clinical studies to assess safety, including long-term safety. Does the Agency agree?

**FDA Response:**
We do not agree. As previously noted, if bioequivalence is not established in the fasted state, you will be required to do an efficacy study. Our predominant concern with your product is the potential for an inconsistent therapeutic effect because the delivery of oxycodone is highly dependent on the meal co-ingested. In addition, you
will be required to assess the effect of a wide range of meals on the safety of the drug. We note that you have cited other products with a food effect, however, those products do not have the same extent of food effect on Cmax and AUC as your product.

Discussion:
See Discussion under Question 1a.

**Question 2.** Does the Agency agree that the preliminary results of this study, the intention to label the product “Take with Food”, and the rationale provided in Section 4.2.3.2 of the Background Information Package sufficiently characterize the effect of food and address the safety of the formulation in light of the potential variability in patients’ diets and or behaviors?

**FDA Response:**
As stated in our advice letter dated December 1, 2009, in follow up to our SPA-No Agreement Letter issued on July 6, 2009 and to your July 21, 2009 correspondence, we reiterate our concern that there may be individuals in whom the PK differences will be substantially greater than the observed average difference and a failure to adhere to the same food-related dosing conditions could represent a safety concern and even a risk for unintended overdose. Whether or not a “take with food” instruction will be sufficient to adequately address this concern will depend on the results of your study. Therefore, as previously noted, it will be necessary to carefully collect data on the meals eaten, the timing of dosing, and the subsequent efficacy and safety.

Discussion:
See Discussion under Question 1a.

**Question 3a.** Are the two bioavailability/bioequivalence studies (CP-OXYDET-09 and CPOXYDET-10) that compare the Oxycodone DETERx formulation with OxyContin adequate bridging studies to provide a basis for reliance upon the Agency’s finding of safety and efficacy of OxyContin?

**FDA Response:**
Study CP-OXYDET-09 will provide the relative bioavailability linkage needed to support your 505(b)(2) New Drug Application (NDA) relying on the previous findings of safety and efficacy of OxyContin. Study CPOXYDET-10 will provide multiple-dose pharmacokinetic data of your product relative to OxyContin and will provide useful data to assess the extended-release characteristics of your product. However, as stated in our response to question 1a, your product is not considered bioequivalent to OxyContin since the PK characteristics do not meet bioequivalence criteria under fasting conditions and the proposed bioavailability/bioequivalence (BA/BE) studies are inadequate to act as the sole basis for extrapolating safety and efficacy.
Discussion:
There was no further discussion on this point.

**Question 3b.** Does the Agency agree that the above pharmacokinetic studies will generate all of the pharmacokinetic and bioavailability data needed to support the NDA?

**FDA Response:**
Adequacy of the pharmacokinetic studies submitted at the time of NDA submission will be a review issue.

Discussion:
There was no further discussion on this point.

**Question 4.** Collegium is aware that Purdue Pharma, L.P. has submitted an NDA (NDA-22-272) for a new formulation of OxyContin. The bridging studies for Oxycodone DETExRx (see Question 2 above) include the currently marketed OxyContin formulation, as listed in the Orange Book. If the current OxyContin formulation is substituted with the new formulation but is still listed in the Orange Book at the time of the Oxycodone DETEx NDA submission, will the Collegium bridging studies (CP-OXYDET-09 and CP-OXYDET-10) still be valid? Alternatively, if the current OxyContin formulation is no longer listed in the Orange Book at the time of the submission of the Oxycodone DETEx NDA, will the Collegium bridging studies still be valid?

**FDA Response:**
We believe your proposed relative bioavailability studies will still be sufficient to provide the scientific bridge necessary in order to reference the Agency’s prior findings for OxyContin if a new formulation is approved and replaces the currently marketed OxyContin in the Orange Book.

Discussion:
There was no further discussion on this point.

**Question 5.** If the Agency does not agree that an acceptable clinical bridge to OxyContin has been established with the proposed plan of submitting an NDA for this product under Section 505(b)(2) supported solely by pharmacokinetic studies (as outlined in Questions 1 and 2), Collegium will then conduct a 12-week safety and efficacy study in a relevant patient population. A protocol describing this study was submitted to the Agency with a Request for Special Protocol Assessment on May 21, 2009. In the March 8, 2007 PIND Meeting, the Agency indicated that:

“A safety assessment beyond the data from the efficacy study would not likely be needed.”

Thus, if Collegium is required to conduct the 12-week safety and efficacy study as outlined in the final approved SPA, no additional long term safety studies would be conducted. Does the Agency agree?
FDA Response:
See response to Question #1. Also, we note that there was no final agreement on the SPA.

Discussion:
The Sponsor requested clarification as to whether there is additional safety information required outside the 12-week study. The Division stated that, barring any unforeseen safety signals, there would not be a requirement for an additional safety study.

Question 6. Oxycodone DETERx meets the definition of a modified-release beaded capsule as outlined in the FDA Guidance, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products- General Considerations, dated March 2003; the product strength differs only in the number of beads containing the active moiety. Therefore, consistent with the Guidance, Collegium has conducted in vitro dissolution using all dosage strengths of Formulation G, the to-be-marketed formulation, to demonstrate dose proportionality. Specifically, dissolution profiles have been generated for each strength using an acceptable dissolution method and the f2 test has been used to confirm that the profiles are similar (i.e., f2 value ≥ 50). All of this data is being submitted in the Background Information Package. Since the f2 value ≥ 50 criterion has been met across the three strengths, a waiver of the in vivo dose proportionality studies is requested.

Does the Agency agree to grant the waiver?

FDA Response:
Yes, we agree with your proposal. The granting of the biowaiver is a review issue that will be based on comparability of the dissolution profiles across the different strengths in three media.

Discussion:
The Sponsor asked if there was any reason they would not be granted a biowaiver. The Division stated that the data presented in the briefing package would support a biowaiver; however, final determination must be made based upon the final dissolution methods. If the data from the final dissolution method appears the same as the data presented, then a biowaiver would likely be granted.

Question 7. The in vitro alcohol interaction data demonstrates that none of the proposed dosage strengths of the to-be-marketed Oxycodone DETERx formulation exhibit dose dumping; therefore, a waiver of alcohol interaction in vivo studies is requested. Does the Agency agree to grant the waiver?

FDA Response:
We have not reviewed these data in detail and, hence, cannot conclude with certainty that the in vitro data did not demonstrate dose dumping. In addition to the visual inspection of dissolution profiles for dose dumping, perform an f2 test to confirm similarity in dissolution profiles. However, based on your assessment that
Discussion:
The Sponsor asked when it would be notified whether an in vivo study would be required. The Division explained that, similarly to our response to Question 6, the final dissolution method is necessary to make any final determination on what is required for this product. The Sponsor inquired about the utility of the f2 test because, for their product, release is lower when tested with alcohol. The Division indicated that an f2 test, in addition to visual inspection, normally serves as a measure for dose dumping. It is possible that the f2 test may not be relevant for the proposed product. It would be acceptable to propose a rationale not to add f2 test results.

Question 8. Although the Oxycodone DETERx formulation may have some specific advantages for pediatric patients in terms of titration and ease of swallowing, Collegium intends to request that pediatric studies in children ages 2 to 17 years be deferred as a post-marketing requirement so that the product may first be approved for adults. Until these studies are completed, Collegium would request that the label state: ”Does the Agency agree with this approach?"

FDA Response:
We agree with the waiver for ages birth to less than 2 years of age. However, there is no rationale at this time for deferring studies in children ages 2 to 17 years until after this product is approved in adults.

The Pediatric Research Equity Act (PREA) requires new drug applications to contain a pediatric assessment unless the applicant has obtained a waiver or deferral. The Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it must address whether and, if so, under what grounds, the applicant plans to request a waiver and/or deferral under PREA. Applicants are encouraged to submit their pediatric plans to the Agency as early as possible in the drug development process and to discuss these plans with the Agency at critical points in the development process for a particular drug or biologic. Refer to the Draft Guidance for Industry “How to Comply with the Pediatric Research Equity Act” for further information.

Discussion:
The Sponsor requested confirmation that there is no requirement to study their drug in pediatrics prior to the submission of the NDA. The Division explained that the Sponsor should start developing an age-appropriate formulation and study protocols, and provide an update as to the status at the time of NDA submission. The Division stated that the Agency is reevaluating PREA requirements for opioids and that the Sponsor will be required to demonstrate efficacy for children less than 2 years of age, and obtain PK, dosing and safety data for patients over 2 2 years of age.
Question 9a. In the March 8, 2007 PIND Meeting, the Agency stated: “If appropriate, information regarding aspects of your formulation and its purported abuse deterrent properties may be included in appropriate sections of the product label.”

Assuming data for chewing the Oxycodone DETERx Formulation G capsule contents confirms the findings of previous pharmacokinetic studies, Collegium proposes to provide the pharmacokinetic data for the chewed and intact formulation in the Pharmacokinetics and Metabolism section of the prescribing information. Does the Agency agree with this approach?

FDA Response:
Labeling is an NDA review issue. However, depending on the scientific rigor and design of the proposed studies and the results obtained, inclusion of the pharmacokinetic data for the chewed and intact formulation may be acceptable. Your current proposal is to study the PK of the product after chewing for 60 seconds and consumption with food. It is important that the chewing paradigm you employ in this study captures the worst case scenario. Additionally, include a cohort of subjects receiving the product after chewing under fasting condition.

Discussion:
The Sponsor stated that they consider chewing for 60 seconds a worst-case scenario. The Division stated that they expect more severe conditions tested, such as grinding and harsh dissolution conditions, to evaluate whether the extended-release properties can be defeated. If the Sponsor can demonstrate they are measuring the worst-case scenario for the product, then it would be likely that the statement can be removed from the Warnings Section of the FPI.

The Sponsor requested clarification as to why conditions under fasting should be tested if the product will be taken with food. The Division indicated that, since consumption of food results in greater exposure to the drug, it may mask any effect chewing might have on the formulation. Hence, the Division recommends that a cohort of subjects should receive the crushed product in the fasted condition to confirm a lack of effect from crushing.

Question 9b. Collegium believes that this data also supports adding the following to the Dosage and Administration section of the label: Does the Agency agree with this approach?
FDA Response:
If there are adequate PK data to support the safety of administering Oxycodone DETERx after the capsule has been manipulated, labeling for alternate methods of administration may be suitable. However, you will need additional studies to support this.

The reliability of transfer of capsule contents through the nasogastric tube must be evaluated in order to support labeling claims. This can be conducted using an in vitro study. In addition, the product integrity after passing through the nasogastric tube will need to be evaluated in vitro. This may be accomplished by evaluating dissolution characteristics of the capsule contents before and after passing through gastrostomy tubes of different dimensions (inner diameter/outer diameter).

Similarly, to support labeling for administering sprinkled contents of the capsule, usually done by putting the material in a soft food substance, as an alternative to swallowing the capsule whole, you will need to evaluate the effects of food on the sprinkled contents.

Discussion:
There was no further discussion on this point.

Question 10. In the March 8, 2007 PIND Meeting, the Agency stated: “A lack of effect of chewing on the PK profile will not be sufficient to exclude all boxed warnings of abuse potential. However, the warnings about risk related to chewing can be amended or deleted if the PK study results support such changes.” Collegium Protocols CP-OXYDET-01 and CP-OXYDET-02 confirmed that the pharmacokinetic profiles of intact capsules and chewed capsule contents were bioequivalent. Collegium considers chewing the capsule contents to be at least as rigorous as other forms of physical manipulation (e.g., breaking, crushing). Supporting rationale and data regarding the influence of breaking and various methods of crushing is summarized in the Background Information Package. Based on this rationale and data, in addition to “chewing”, Collegium proposes excluding the section of the Black Box Warning relating to “breaking” and “crushing” of the product. Specifically, assuming data for chewing Formulation G capsule contents (CP-OXYDET-12) confirms the findings of the previous pharmacokinetic studies, Collegium proposes excluding the following from the Black Box Warning from the OxyContin label: “[Dosage Forms] are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed [Dosage Forms] lead to rapid release and absorption of a potentially fatal dose of oxycodone.” Does the Agency agree with this approach?

FDA Response:
Depending on the scientific rigor and design of the proposed studies and the results obtained, language related to chewing, breaking and crushing may be excluded from the Box Warning.
Discussion:
There was no further discussion on this point.

NONCLINICAL

Question 11. It is proposed that no further pre-clinical or clinical assessments of the safety of any of the inactive ingredients in the DETERx formulation will be conducted. Does the Agency agree?

FDA Response:
Your approach appears acceptable; however, the adequacy of your justification can only be determined upon review of the NDA. The FDA Inactive Ingredients Database lists levels of excipients for a single unit only. Refer to the maximum theoretical daily dose for oxycodone in an opioid tolerant individual when determining whether an excipient is considered novel.

Any novel excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following address:

As noted in the document cited above, “the phrase new excipients means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.” (emphasis added).

Discussion:
The Division stated that the Sponsor should submit a justification of the safety of the excipients including literature references and other publicly available data to the IND for consideration, although the Division cannot promise it will be reviewed prior to NDA submission. The Sponsor was also advised to include copies of the references used to support their justification in the submission.

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 12. Collegium intends to procure the drug substance, Oxycodone Base, and employ the regulatory specifications as set forth in the drug substance DMF. The Manufacturer’s regulatory
FDA Response:
We do not agree. The maximum theoretical daily dose (MTDD) for an opioid-tolerant individual must be considered in order to determine the ICH guideline qualification thresholds for impurity and degradant levels. Refer to our response to Question 16 for the MTDD of oxycodone in an opioid tolerant individual.

For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICH Q3A(R), ICH Q3B(R)).

- Adequate qualification must include:
  - Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
  - Repeat dose toxicology of appropriate duration to support the proposed indication.

- In module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICHQ3A and Q3B qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

- NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity that exceeds ICH qualification thresholds.

- Potentially genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic impurities in the drug substance and drug product unless otherwise adequately justified. Adequate safety qualification for any potential genotoxic impurities identified via a structural alert for mutagenicity must be provided with the NDA submission and must include and in vitro bacterial reverse mutation assay (Ames assay) with the isolated impurity, tested up to the limit dose for the assay. Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification may require an
assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

 NOTE: We may to refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity containing a structural alert for mutagenicity that exceeds 1.5 mcg/day.

Note also that you may use specification for the drug substance only if a review of the DMF, including the proposed specification, is found adequate to support the Oxycodone DETErx NDA.

Discussion:
The Sponsor asked, if the drug substance specifications for their product impurities were set at ppm would that be acceptable. The Division explained that the only information that can be relied upon in a 505(b)(2) application is what is available in the label of the RLD and this information is not listed in the label. However, the Division noted that approval of this opioid product would not be held up if the product meets the ppm for impurity as this represents reasonable current technological capabilities. However, as technological capabilities improve, ultimately the Agency is working toward reaching the NMT 1.5 mcg/day specifications for impurities that are genotoxic structural alerts.

Question 13. Collegium intends to control the level at the API level by working with the DMF holder to have incoming API (drug substance) specifications that meet FDA defined specification of NMT %. Therefore, Collegium does not intend to include a specification for the drug product release and stability testing. Does the Agency agree?

FDA Response:
We agree that a specification in the drug product may not be necessary but this will be a review issue in the NDA.

Discussion:
The Division further clarified that the Sponsor should provide data to demonstrate that is not increasing in the drug product. The Sponsor stated that the API supplier controls the level in the drug substance. The Division agreed that a specification for the drug product would not be necessary.

Question 14. A enclosure collection system complies with FDA 21 CFR. This enclosure collection system has been used at the contract manufacturer for manufacturing development, clinical and registration batches. Collegium intends to use this same
enclosure collection system for both validation and commercial batch manufacturing. Does the Agency agree with this plan?

FDA Response:
The use of the same collection system seems reasonable, but ultimately whether or not the system is acceptable is a review issue. Note also that the collection system, as well as the other equipment, will have to be approved by our field inspection team prior to commercialization.

Discussion:
There was no further discussion on this point.

Question 15. Formulation G has now been selected for use in pharmacokinetic studies in support of the NDA. Formulations F and G differed in approach? Does the Agency agree with this approach?

FDA Response:
We agree with this approach.

Discussion:
There was no further discussion on this point.

Question 16. Reporting, Identification, Qualification. Does the Agency agree with this MDD and Threshold calculation approach?

FDA Response:
We disagree with your MDD and Threshold calculation approach. Due to the development of tolerance to the effects of opioids, there is no maximum daily dose for these products. We will consider the maximum theoretical daily dose (MTDD) for an opioid tolerant individual for your drug product when establishing the safety
qualification threshold for impurities, degradants, and the safety of the proposed excipients in your drug product. Based on clinical use data, the MTDD of oxycodone in an opioid tolerant individual is 1.5 g/day.

Discussion:
There was no further discussion on this point.

Question 17. Oxycodone DETERx Capsules contain a hydrophobic fatty acid/wax based formulation. The in vitro dissolution methods described in the FDA Dissolution Database and the USP for Oxycodone Hydrochloride Extended Release are not appropriate for Oxycodone DETERx Capsules due to the formulation’s hydrophobic nature. Collegium, therefore, proposes to submit and justify a new in vitro dissolution medium and a three-point dissolution specification which specifically addresses the properties of the Oxycodone DETERx Capsules formulation. Does the Agency concur with the rationale for selecting the apparatus, medium, rotation speed, and sampling time points and agree with this dissolution specification and acceptance criteria setting approach?

FDA Response:
You need to submit a full dissolution method development report to justify the choice of apparatus, rotation speed, and dissolution medium. Include a justification of the concentration of surfactant used. Provide dissolution profiles with and without surfactants to demonstrate the effect of the surfactant on the release characteristics of your formulation.

Discussion:
There was no further discussion on this point.

Question 18. Aside from the specific Drug Product release specifications questions raised in Questions 15, 16 and 17 above, does the Agency agree that the proposed approach to the Drug Product release specifications as described in the Background Information Package are suitable and adequate for the remainder of the specifications, i.e. appearance, identification, assay, content uniformity, residual solvents, and microbial limits?

FDA Response:
We agree that the release specifications should include appearance, identification, assay, content uniformity, and residual solvents. Test the finished drug product at release and on stability for Microbial Limits as per USP <61> if your studies show microbial growth in the drug product at the upper limit of your specification.

The dosage form is an HPMC (hydroxypropyl methylcellulose) hard capsule filled with micron-sized beads containing a formulation of the oxycodone drug substance, beeswax and carnuba wax, and myristic acid.
Development batches on lab scale, and pilot scale were manufactured at a Contract Research Organization (CRO). The commercial contract manufacturing (CMO) site will be used. It is noted that was not specified.

The proposed release and stability specifications for the drug product do not include an assay for microbial limits. There is also no specification in Section 6.2.9.8 of the meeting package, you state that,

In addition, you propose to conduct,

In order to support the omission of routine microbial limits testing at release and during stability, submit the following in the NDA:

1. Data demonstrating a history of a low microbial load in the drug product as demonstrated by performing microbial limits testing (USP<61>) at release for, at a minimum, three submission batches from the commercial manufacturing site. Actual data (microbial counts) should be provided, and not simply a designation of “passed.” Details of the test methods should include sample size, preparation and dilutions, as well as the inoculation volumes and final cultivation methods (e.g., ).

2. A demonstration that the drug product does not support microbial growth (especially mold species) either by using direct microbial challenge studies for example, samples of the submission batches from the commercial manufacturing site

3. A description of the manufacturing controls for the process and for the manufacturing facility which are designed to control the sources of potential microbial contamination of the drug product. Such controls would include:
   a. an established environmental monitoring program;
   b. an established equipment cleaning program; and
   c. raw materials controls to include periodic microbial limits testing plus an acceptable vendor audit program.

In addition, from a stability standpoint, you should submit the results at release and at expiry for the long term storage conditions and at release and at six months storage under accelerated conditions.
Finally the release and stability specifications should include a statement under the heading of Microbial Limits that it is "not required" with a footnote stating that, "if tested, the product will meet the recommended limits in USP<1111>.”

Discussion:
There was no further discussion on this point.

Question 19. Oxycodone DETERx Capsules are being developed in multiple strengths (10 mg, 20 mg, and 40 mg Oxycodone HCl Equivalent Strengths). Collegium proposes a stability testing protocol agree?

FDA Response:
We do not accept your approaches for stability testing for these non-typical tamper resistant drug products. Your protocol should provide for testing

Discussion:
There was no further discussion on this point.

Question 20. Collegium proposes to submit the NDA with no less than six (6) months of long-term and accelerated stability from registration batches and up to twelve (12) months of long-term stability from other GMP development batches, with additional stability data submitted at appropriate times when the testing is complete for the subsequent intervals. Does the Agency agree?

FDA Response:
We strongly recommend that you submit the maximum available stability data for your primary stability batches at the time of NDA submission. While every effort will be made to review any stability amendments to the NDA, their review will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, per Good Review Management Principle (GRMP) guidelines, we may not be able to review amendments submitted to the NDA during the review cycle. Accordingly, you run the risk of being granted a shortened expiry.

Discussion:
There was no further discussion on this point.

Question 21. A study outline, consistent with guidance obtained in the March 8, 2007 PIND Meeting as well as the January 2010 FDA Draft Guidance entitled, Assessment of Abuse Potential of Drugs, to assess oxycodone extractability from the Oxycodone DETERx Capsules under a variety of in vitro conditions has been designed as outlined in the Background Information Package. Does the Agency agree that the Extraction Study design is acceptable?

FDA Response:
This response will be provided in a post-meeting note in our minutes.

Discussion:
There was no further discussion on this point.

POST-MEETING NOTE:

We do not agree that the Extraction Study design is acceptable. We have the following comments regarding your submitted information in the briefing package:

1. A detailed protocol regarding "6.2.11 Solvent Extractability" has not been provided. CSS will review the detailed protocol when it is submitted and then provide comments.

2. Clarification is required regarding exactly what formulation is to be assessed. Extraction studies must be conducted on the to-be-marketed product.

3. The mechanical crushing and grinding studies reported in the Background Information Package were not done on the to-be-marketed product formulation. As such, the to-be-marketed formulation needs to be examined for “crushing” and “grinding” using various available tools ranging from two spoons to coffee grinders.

4. Extraction of API from intact and tampered samples should be monitored at least to 24 hours or until the entire API is extracted. Time points for solvent sampling should be selected to adequately characterize the extraction of API as a function of time.

5. Agitation should be continuous during the extraction phase for all parts of the extractability studies.

6. Methanol and isopropyl alcohol should be included as solvents along with acetone and ethyl acetate.

7. The extractability protocol for Part 4 should also be performed on the “Intact capsule contents” and not just the “Crushed capsule contents.”

ADDITIONAL COMMENTS

NONCLINICAL
We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry “Applications Covered by Section 505(b)(2)” available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency’s interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at
If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Discussion:
There was no further discussion on this point.

**ACTION ITEMS:**

1. The Sponsor will propose a meal that would represent the low-fat range of what an individual could characterize as a “meal.” That meal will be tested in a food effect study to determine whether this low-end range meal results in the pharmacokinetic profile observed with the high-fat meal. If the low-end range meal results in similar pharmacokinetics, food consumption data in Phase 3 can be limited to a binary “yes/no” answer to the question of whether the drug was administered with a meal.

2. The Sponsor plans to resubmit their SPA with additional food effect data.

3. No long-term safety information will be required barring any unforeseen safety signals.

4. The alcohol interaction study on the drug product can be submitted prior to the NDA submission, but must be completed using the final dissolution method.

5. The Sponsor acknowledges that PREA studies must be considered and developed, but not necessarily initiated, prior to submission of the NDA.

6. An impurity specification of \[^{\text{(b) (4)}}\] ppm \[^{\text{(b) (4)}}\] in the drug substance will not be an approvability issue.

7. No specification will be required \[^{\text{(b) (4)}}\] in the drug product because it is not a degradant and it is controlled by the API supplier in the drug substance.
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/s/

KATHLEEN M DAVIES
04/29/2010