CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
208090Orig1s000

OTHER REVIEW(S)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

**NDA #** 208090  
**Product Name:** XTAMPZA ER (oxycodone extended release capsules)  
**PMR Description:**

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>10/2019</td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td>3/2020</td>
</tr>
</tbody>
</table>

1. **During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement.** Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

3. If the study/clinical trial is a PMR, check the applicable regulation. If not a PMR, skip to 4.

- Which regulation?
  - Accelerated Approval (subpart H/E)
  - Animal Efficacy Rule
  - Pediatric Research Equity Act
  - FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - Analysis of spontaneous postmarketing adverse events?
    - Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - Analysis using pharmacovigilance system?
    - Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3922113
The initial type of study that would be anticipated would be a prospective epidemiological study to measure the incidences of the adverse outcomes listed above. However, tools to measure both the risk factors and outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?
There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the
safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________
(signature line for BLAs)
## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

<table>
<thead>
<tr>
<th>NDA #</th>
<th>208090</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>XTAMPZA ER (oxycodone extended release capsules)</td>
</tr>
</tbody>
</table>

### PMR Description:

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>Metric</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>11/2014</td>
</tr>
<tr>
<td>Study Completion</td>
<td>4/2019</td>
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<tr>
<td>Final Report Submission</td>
<td>9/2019</td>
</tr>
</tbody>
</table>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term use of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

3. If the study/clinical trial is a PMR, check the applicable regulation. 
   If not a PMR, skip to 4.
   - Which regulation?
     □ Accelerated Approval (subpart H/E)
     □ Animal Efficacy Rule
     □ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
     ☒ Assess a known serious risk related to the use of the drug?
     □ Assess signals of serious risk related to the use of the drug?
     □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
     □ Analysis of spontaneous postmarketing adverse events?
       Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     □ Analysis using pharmacovigilance system?
       Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, neither the codes for many of the risk factors nor those for these outcomes have been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Reference ID: 3922113
5. Is the PMR/PMC clear, feasible, and appropriate?

- ✔ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ✔ Are the objectives clear from the description of the PMR/PMC?
- ✔ Has the applicant adequately justified the choice of schedule milestone dates?
- ✔ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

**If so, does the clinical trial meet the following criteria?**

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

Required

- ☒ Observational pharmacoepidemiologic study
- ☒ Registry studies
- ☒ Primary safety study or clinical trial
- ☒ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☒ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☒ Drug interaction or bioavailability studies or clinical trials
- ☒ Dosing trials

(Continuation of Question 4)

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
  (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- ☐ Other
PMR/PMC Development Coordinator:

☑ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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(signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

*The data needed to validate measures and outcomes of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.*

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

*A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.*

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.
3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [x] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey to identify patients that misuse and/or abuse opioids, and conducting an interview, chart review, or a similar activity to determine if the patients understand the survey instrument, and if the instrument measures what is designed to assess.

- [x] Required
  - [ ] Observational pharmacoepidemiologic study
  - [ ] Registry studies
  - [ ] Primary safety study or clinical trial
  - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - [ ] Thorough Q-T clinical trial
  - [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - [ ] Pharmacokinetic studies or clinical trials
  - [ ] Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

*Continuation of Question 4*

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
  (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

**PMR/PMC Development Coordinator:**

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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(signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.

   **If not a PMR, skip to 4.**
   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [x] FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [x] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

     - [ ] Analysis using pharmacovigilance system?
       **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   An observational study would likely be conducted that includes identifying patients who fulfill the criteria of long-term opioid use, administering a specifically designed survey instrument to identify opioid abuse and misuse behaviors, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

   **Required**
   - [x] Observational pharmacoepidemiologic study
   - [ ] Registry studies
   - [ ] Primary safety study or clinical trial
   - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [ ] Thorough Q-T clinical trial
   - [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   - [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - [ ] Pharmacokinetic studies or clinical trials
   - [ ] Drug interaction or bioavailability studies or clinical trials
   - [ ] Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ✓ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ✓ Are the objectives clear from the description of the PMR/PMC?
   ✓ Has the applicant adequately justified the choice of schedule milestone dates?
   ✓ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

   If so, does the clinical trial meet the following criteria?

   ☐ There is a significant question about the public health risks of an approved drug
   ☐ There is not enough existing information to assess these risks
   ☐ Information cannot be gained through a different kind of investigation
   ☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
   ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
   ✓ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

   (signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #  208090  
Product Name:  XTAMPZA ER (oxycodone extended release capsules)

PMR Description:  
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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need  
☐ Life-threatening condition  
☒ Long-term data needed  
☐ Only feasible to conduct post-approval  
☐ Prior clinical experience indicates safety  
☐ Small subpopulation affected  
☐ Theoretical concern  
☐ Other

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.
3. If the study/clinical trial is a PMR, check the applicable regulation.
   **If not a PMR, skip to 4.**

   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [X] FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [X] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

     - [ ] Analysis using pharmacovigilance system?
       **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - [X] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey instrument (PRISM-5-Op) to identify those with prescription opioid Substance Use Disorder and addiction, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

   **Required**
   - [X] Observational pharmacoepidemiologic study
   - [ ] Registry studies
   - [ ] Primary safety study or clinical trial
   - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [ ] Thorough Q-T clinical trial
   - [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   - [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - [ ] Pharmacokinetic studies or clinical trials
   - [ ] Drug interaction or bioavailability studies or clinical trials
Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)
☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☑ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☑ Are the objectives clear from the description of the PMR/PMC?
   ☑ Has the applicant adequately justified the choice of schedule milestone dates?
   ☑ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
☑ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________
(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for _each_ PMR/PMC in the Action Package.

**NDA #** 208090  
**Product Name:** XTAMPZA ER (oxycodone extended release capsules)

**PMR Description:** 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need  
- [ ] Life-threatening condition  
- [x] Long-term data needed  
- [ ] Only feasible to conduct post-approval  
- [ ] Prior clinical experience indicates safety  
- [ ] Small subpopulation affected  
- [ ] Theoretical concern  
- [ ] Other

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, algorithms must be developed to reliably identify opioid-related adverse events of misuse, abuse, addiction, overdose and death solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED).
3. If the study/clinical trial is a PMR, check the applicable regulation. If not a PMR, skip to 4.

- Which regulation?
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - [x] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - [ ] Analysis of spontaneous postmarketing adverse events?
    - Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?
    - Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes developing a process or algorithm to reliably identify patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for the opioid-related adverse events of overdose and death, and validating that process or algorithm with chart review or a similar activity.

Required
- [x] Observational pharmacoepidemiologic study
- [ ] Registry studies
- [ ] Primary safety study or clinical trial
- [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- [ ] Thorough Q-T clinical trial
- [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- [ ] Pharmacokinetic studies or clinical trials
- [ ] Drug interaction or bioavailability studies or clinical trials
- [ ] Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

   If so, does the clinical trial meet the following criteria?

   ☐ There is a significant question about the public health risks of an approved drug
   ☐ There is not enough existing information to assess these risks
   ☐ Information cannot be gained through a different kind of investigation
   ☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
   ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
   ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [x] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events of misuse, abuse, addiction, overdose, and death need to be validated.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
   *If not a PMR, skip to 4.*

   - **Which regulation?**
     
     - Accelerated Approval (subpart H/E)
     - Animal Efficacy Rule
     - Pediatric Research Equity Act
     - FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     
     - [x] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     
     - [ ] Analysis of spontaneous postmarketing adverse events?  
       *Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk*

     - [ ] Analysis using pharmacovigilance system?  
       *Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk*

     - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
       *Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk*

     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   **An observational study would likely be conducted that includes identifying patients with a specifically developed algorithm solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse abuse, and addiction, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition. The validation process would be conducted in multiple data resources to ensure applicability in diverse populations and settings.**

   **Required**

   - [x] Observational pharmacoepidemiologic study
   - [ ] Registry studies
   - [ ] Primary safety study or clinical trial
   - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [ ] Thorough Q-T clinical trial
   - [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   - [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - [ ] Pharmacokinetic studies or clinical trials
Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

__________________________

(signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>03/2015</td>
</tr>
<tr>
<td>Study Completion</td>
<td>10/2017</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>01/2018</td>
</tr>
</tbody>
</table>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [X] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - [x] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - [ ] Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<table>
<thead>
<tr>
<th>An observational study would likely be conducted that includes identifying patients who were prescribed opioids and conducting chart reviews or similar activities to determine if there is a pattern of activity suggestive of doctor and/or pharmacy shopping and identify common characteristics of those patients.</th>
</tr>
</thead>
</table>

**Required**

- [x] Observational pharmacoepidemiologic study
- [ ] Registry studies
- [ ] Primary safety study or clinical trial
- [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- [ ] Thorough Q-T clinical trial
- [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- [ ] Pharmacokinetic studies or clinical trials
- [ ] Drug interaction or bioavailability studies or clinical trials
- [ ] Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☑ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☑ Are the objectives clear from the description of the PMR/PMC?
   ☑ Has the applicant adequately justified the choice of schedule milestone dates?
   ☑ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

   If so, does the clinical trial meet the following criteria?

   ☑ There is a significant question about the public health risks of an approved drug
   ☑ There is not enough existing information to assess these risks
   ☑ Information cannot be gained through a different kind of investigation
   ☑ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
   ☑ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
   ☑ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

   (signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [x] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| An observational study would likely be conducted that includes identifying patients who meet one or more definitions of doctor and/or pharmacy shopping, and then conducting chart review or a similar activity to determine whether the identified patients have an indication of opioid misuse and/or abuse. |

**Required**

- [x] Observational pharmacoepidemiologic study
- [ ] Registry studies
- [ ] Primary safety study or clinical trial
- [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- [ ] Thorough Q-T clinical trial
- [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- [ ] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- [ ] Pharmacokinetic studies or clinical trials
- [ ] Drug interaction or bioavailability studies or clinical trials
- [ ] Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ✗ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ✗ Are the objectives clear from the description of the PMR/PMC?
   ✗ Has the applicant adequately justified the choice of schedule milestone dates?
   ✗ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

   If so, does the clinical trial meet the following criteria?

   ☐ There is a significant question about the public health risks of an approved drug
   ☐ There is not enough existing information to assess these risks
   ☐ Information cannot be gained through a different kind of investigation
   ☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
   ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
   ✗ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

   (signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
   - [ ] Unmet need
   - [x] Life-threatening condition
   - [ ] Long-term data needed
   - [ ] Only feasible to conduct post-approval
   - [ ] Prior clinical experience indicates safety
   - [ ] Small subpopulation affected
   - [ ] Theoretical concern
   - [ ] Other

   The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

   A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

   The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the relationship between doctor/pharmacy shopping and misuse, abuse, and/or addiction needs to be more clearly elucidated.
3. If the study/clinical trial is a PMR, check the applicable regulation.  

*If not a PMR, skip to 4.*

- **Which regulation?**
  - □ Accelerated Approval (subpart H/E)
  - □ Animal Efficacy Rule
  - □ Pediatric Research Equity Act
  - □ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - □ Assess a known serious risk related to the use of the drug?
  - □ Assess signals of serious risk related to the use of the drug?
  - □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - □ Analysis of spontaneous postmarketing adverse events?  
  *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - □ Analysis using pharmacovigilance system?  
  *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - □ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
  *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| An observational study would likely be conducted that includes identifying patients who meet one or more definitions of “doctor/pharmacy shopping”, and then conducting chart review or a similar activity to determine whether the patterns and characteristics of behaviors indicative of misuse, abuse, or addiction can also be identified in the patient population. |

**Required**

- □ Observational pharmacoepidemiologic study
- □ Registry studies
- □ Primary safety study or clinical trial
- □ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- □ Thorough Q-T clinical trial
- □ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- □ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- □ Pharmacokinetic studies or clinical trials
- □ Drug interaction or bioavailability studies or clinical trials
- □ Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:
☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☑ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☑ Are the objectives clear from the description of the PMR/PMC?
   ☑ Has the applicant adequately justified the choice of schedule milestone dates?
   ☑ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

   If so, does the clinical trial meet the following criteria?

   ☐ There is a significant question about the public health risks of an approved drug
   ☑ There is not enough existing information to assess these risks
   ☑ Information cannot be gained through a different kind of investigation
   ☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
   ☑ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
   ☑ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

   (signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.
*If not a PMR, skip to 4.*

   - **Which regulation?**
     - [□] Accelerated Approval (subpart H/E)
     - [□] Animal Efficacy Rule
     - [□] Pediatric Research Equity Act
     - [X] FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [X] Assess a known serious risk related to the use of the drug?
     - [□] Assess signals of serious risk related to the use of the drug?
     - [□] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [□] Analysis of spontaneous postmarketing adverse events?
       - **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk
     - [□] Analysis using pharmacovigilance system?
       - **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     - [□] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       - **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk
     - [X] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

   **Required**
   - [□] Observational pharmacoepidemiologic study
   - [□] Registry studies
   - [X] Primary safety study or clinical trial
   - [□] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [□] Thorough Q-T clinical trial
   - [□] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
   - [□] Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
   - [□] Pharmacokinetic studies or clinical trials
   - [□] Drug interaction or bioavailability studies or clinical trials
   - [□] Dosing trials

Reference ID: 3922113
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
  (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 2966-3 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2966-4, 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.

PMR Schedule Milestones:

<table>
<thead>
<tr>
<th>PMR Schedule Milestone</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Draft Protocol Submission</td>
<td>08/2016</td>
</tr>
<tr>
<td>Final Protocol Submission</td>
<td>12/2016</td>
</tr>
<tr>
<td>Study Completion</td>
<td>12/2017</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>06/2018</td>
</tr>
<tr>
<td>Other</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.
   - [ ] Unmet need
   - [ ] Life-threatening condition
2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has determined that the sponsor must conduct individual post-marketing studies of XTAMPZA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the properties of XTAMPZA ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
   **If not a PMR, skip to 4.**
   - **Which regulation?**
     - □ Accelerated Approval (subpart H/E)
     - □ Animal Efficacy Rule
     - □ Pediatric Research Equity Act
     - ★ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - ★ Assess a known serious risk related to the use of the drug?
     - □ Assess signals of serious risk related to the use of the drug?
     - □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - □ Analysis of spontaneous postmarketing adverse events?  
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

     - □ Analysis using pharmacovigilance system?  
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - ★ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Descriptive observational studies to document the patterns of use of Xtampza ER and describe the patterns of misuse and abuse that are occurring in the “real world”.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #: 208090
Product Name: XTAMPZA ER (oxycodone extended release capsules)

PMR Description: 2966-4: 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*.

PMR Schedule Milestones:  Draft Protocol Submission: 08/2018  
Final Protocol Submission: 12/2018  
Study Completion: 12/2020  
Final Report Submission: 06/2021  
Other: N/A

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need  
☐ Life-threatening condition  
☒ Long-term data needed  
☒ Only feasible to conduct post-approval  
☐ Prior clinical experience indicates safety  
☐ Small subpopulation affected  
☐ Theoretical concern  
☐ Other

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of XTAMPZA ER actually deter abuse of the product in “real world” use.
7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has determined that the sponsor must conduct individual post-marketing studies of XTAMPZA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the properties of XTAMPZA ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

8. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [x] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [ ] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - [ ] Analysis using pharmacovigilance system?
    
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
The design of the hypothesis-testing studies for XTAMPZA ER will be informed by the patterns of use and the patterns of misuse/abuse documented in PMR 2966-3. The hypothesis testing studies must incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of XTAMPZA ER. In particular, post-marketing studies for XTAMPZA ER must include individual assessments of all relevant routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of morphine sulfate and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

**Required**
- ☒ Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

*Continuation of Question 4*

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

**Agreed upon:**
- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

- ☐ Other

10. Is the PMR/PMC clear, feasible, and appropriate?
- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

**PMR/PMC Development Coordinator:**

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

__________________________

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:

- Final Protocol Submission: 09/2017
- Study/Trial Completion: 07/2018
- Final Report Submission: 01/2019
- Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable a risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Beeswax, carnauba wax, and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.
3. If the study/clinical trial is a **PMR**, check the applicable regulation. 

*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events? 
    
    **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk
  
  - [ ] Analysis using pharmacovigilance system? 
    
    **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments? 
    
    **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk
  
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   This is a general toxicology study to ascertain the potential impact of beeswax, carnauba wax, and myristic acid when the drug product is dosed up to the MTDD.

   **Required**
   - [ ] Observational pharmacoepidemiologic study
   - [ ] Registry studies
   - [ ] Primary safety study or clinical trial
   - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [ ] Thorough Q-T clinical trial
   - [x] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
  (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

______________________________
  (signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>04/2017</td>
</tr>
<tr>
<td>Study/Trial Completion</td>
<td>02/2018</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>09/2018</td>
</tr>
<tr>
<td>Other</td>
<td>MM/DD/YYYY</td>
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</tbody>
</table>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Beeswax, carnauba wax, and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.
3. If the study/clinical trial is a PMR, check the applicable regulation. 

*If not a PMR, skip to 4.*

- **Which regulation?**
  - □ Accelerated Approval (subpart H/E)
  - □ Animal Efficacy Rule
  - □ Pediatric Research Equity Act
  - □ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - □ Assess a known serious risk related to the use of the drug?
  - □ Assess signals of serious risk related to the use of the drug?
  - □ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - □ Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - □ Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - □ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   | This is a general toxicology study to ascertain the potential impact of beeswax, carnauba wax, and myristic acid when the drug product is dosed up to the MTDD. |

<table>
<thead>
<tr>
<th>Required</th>
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<tbody>
<tr>
<td>□ Observational pharmacoepidemiologic study</td>
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<td>□ Registry studies</td>
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<tr>
<td>□ Primary safety study or clinical trial</td>
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<tr>
<td>□ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety</td>
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<tr>
<td>□ Thorough Q-T clinical trial</td>
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<tr>
<td>□ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)</td>
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</table>
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?
   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
   ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:  Final Protocol Submission: 10/2017
Study/Trial Completion: 04/2018
Final Report Submission: 10/2018
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - □ Accelerated Approval (subpart H/E)
  - □ Animal Efficacy Rule
  - □ Pediatric Research Equity Act
  - ☑ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - □ Assess a known serious risk related to the use of the drug?
  - □ Assess signals of serious risk related to the use of the drug?
  - ☑ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - □ Analysis of spontaneous postmarketing adverse events?
    
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - □ Analysis using pharmacovigilance system?
    
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☑ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - □ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
The study is a fertility and early embryonic development study that examines the effects of a drug on male and female fertility and early embryonic development up to the point of implantation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:

- Final Protocol Submission: 07/2017
- Study/Trial Completion: 01/2018
- Final Report Submission: 07/2018
- Other: MM/DD/YYYY

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [x] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
8. If the study/clinical trial is a PMR, check the applicable regulation. **If not a PMR, skip to 4.**

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☑ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☑ Assess signals of serious risk related to the use of the drug?
  - ☑ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    - **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    - **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☑ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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Beeswax, carnauba wax, and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.

There are some published studies with components of the waxes that suggest adequate safety margins. However, these studies do not test the full spectrum of chemicals present in the drug product formulation. This study is being requested to provide definitive data to characterize the potential impact of these compounds on the developing fetus at high doses.
The study is an embryo-fetal development study in the rat model to assess the potential for teratogenicity.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:

Final Protocol Submission: 09/2017
Study/Trial Completion: 06/2018
Final Report Submission: 12/2018
Other: MM/DD/YYYY

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
Beeswax, carnauba wax, and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.

There are some published studies with components of the waxes that suggest adequate safety margins. However, these studies do not test the full spectrum of chemicals present in the drug product formulation. This study is being requested to provide definitive data to characterize the potential impact of these compounds on the developing fetus at high doses.

13. If the study/clinical trial is a **PMR**, check the applicable regulation. **If not a PMR, skip to 4.**

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?
    **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
The study is an embryo-fetal development study in the rabbit model to assess the potential for teratogenicity.

<table>
<thead>
<tr>
<th>Required</th>
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<tbody>
<tr>
<td>☐ Observational pharmacoepidemiologic study</td>
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<tr>
<td>☐ Registry studies</td>
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<td>☐ Primary safety study or clinical trial</td>
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<td>☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety</td>
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<td>☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)</td>
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<td><em>Continuation of Question 4</em></td>
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<tr>
<td>☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)</td>
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<td>☐ Immunogenicity as a marker of safety</td>
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<tr>
<td>☐ Other (provide explanation)</td>
</tr>
</tbody>
</table>

| Agreed upon: |
| ☐ Quality study without a safety endpoint (e.g., manufacturing, stability) |
| ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events) |
| ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E |
| ☐ Dose-response study or clinical trial performed for effectiveness |
| ☐ Nonclinical study, not safety-related (specify) |
| ☐ Other |

15. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

**PMR/PMC Development Coordinator:**
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:  
- Final Protocol Submission: 06/2018
- Study/Trial Completion: 03/2019
- Final Report Submission: 11/2019
- Other: MM/DD/YYYY

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
18. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- Which regulation?
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - ☐ Analysis of spontaneous postmarketing adverse events?
    - *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    - *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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Beeswax, carnauba wax, and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.

There are some published studies with components of the waxes that suggest adequate safety margins. However, these studies do not test the full spectrum of chemicals present in the drug product formulation. This study is being requested to provide definitive data to characterize the potential impact of these compounds following administration to the mother during the last period of pregnancy and through weaning. This results in *in utero* exposure and likely exposures via the breast milk. The endpoints evaluate the early growth, survival, and development of the offspring.

Reference ID: 3922113
19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a pre- and post-natal developmental toxicology study in the rat model.

Required
- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:
- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

20. Is the PMR/PMC clear, feasible, and appropriate?
- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2018
Study/Trial Completion: 03/2021
Final Report Submission: 03/2022
Other: MM/DD/YYYY

21. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☑ Prior clinical experience indicates safety
☐ Small subpopulation affected
☑ Theoretical concern
☐ Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

22. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
23. If the study/clinical trial is a PMR, check the applicable regulation. 

If not a PMR, skip to 4.

- Which regulation?
  - Accelerated Approval (subpart H/E)
  - Animal Efficacy Rule
  - Pediatric Research Equity Act
  - FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

24. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
The study is standard carcinogenicity study in the rat model designed specifically to evaluate the carcinogenic potential of these compounds.

Required
- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:
- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

25. Is the PMR/PMC clear, feasible, and appropriate?
- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/2018
Study/Trial Completion: 04/2021
Final Report Submission: 04/2022
Other: MM/DD/YYYY

26. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Although there are limited to no oral toxicology data for beeswax, carnauba wax, and myristic acid, there is human experience with food grade waxes and myristic acid is part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

27. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
Beeswax, carnauba wax and myristic acid have been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The waxes are also complex chemical mixtures that have not been completely characterized. As such, there are not adequate data to support their safety at the MTDD of oxycodone. Some components of the waxes have been reported to cause histiocytosis of mesenteric lymph nodes, histopathological changes in the liver, and it is possible that there will be changes in the pancreas and bile ducts given the attempt to digest these waxes. Full characterization should be completed to reassess the dosing restrictions.

Long-term animal studies in two species to evaluate the carcinogenic potential of a new excipient are standard requirements for drug products with a chronic indication. Based on published summary information, there would appear to be minimal, if any risk of carcinogenicity of these compounds. The study would address the potential carcinogenic impact of these novel excipients.

28. If the study/clinical trial is a PMR, check the applicable regulation. 
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - [ ] Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

29. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
The study is standard carcinogenicity study in the mouse model designed specifically to evaluate the carcinogenic potential of these compounds.

Required
- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:
- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

30. Is the PMR/PMC clear, feasible, and appropriate?
- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Development Template

NDA 208090

PMR/PMC Description: 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 in beeswax, 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.

PMR/PMC Schedule Milestones:

Final Protocol Submission: 10/2016
Study/Trial Completion: 07/2017
Final Report Submission: 09/2017
Other: ______________________________ MM/DD/YYYY

31. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

Although there are limited to no oral toxicology data for beeswax, there is human experience with food grade beeswax as part of the normal diet. Based on previous human experience, a favorable risk-benefit assessment for this drug product, and the dosing limitations listed in the drug product labeling, this study was considered appropriate to be completed post-marketing. Once completed, the dose restrictions in the labeling would be reconsidered.

32. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
33. If the study/clinical trial is a PMR, check the applicable regulation. If not a PMR, skip to 4.

- Which regulation?
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - [ ] Analysis of spontaneous postmarketing adverse events?
    
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - [ ] Analysis using pharmacovigilance system?
    
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

34. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Beeswax has been used in FDA-approved drug products at low levels. However, when used up to the maximum theoretical daily dose (MTDD) of oxycodone, the levels of each of these excipients would exceed that of normal dietary consumption. The beeswax is a very complex chemical mixture that has not been completely characterized, and these natural products could contain a diverse array of potential contaminants, including antibiotics, pesticides, fungicides, heavy metals, and leachables from the bee hive itself. These are probably present in food grade materials; however, as the dose of the drug at the MTDD will increase levels of beeswax above that in the diet, more detailed analysis should be completed and limits imposed if necessary. The risk will depend upon what is identified.

Reference ID: 3922113
This is an analytical chemistry study that entails development of methodology to characterize the potential impurities in beeswax, such as heavy metals, pesticides, fungicides, antibiotics, and leachables from the bee hive itself. The study will be completed on the beeswax used to manufacture the drug product. In the final study report, a toxicology risk assessment and proposals for specifications must be submitted.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

35. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
☐ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

...................................................................................

(signature line for BLAs)
PMR/PMC Description: Conduct a study to characterize the levels of \textsuperscript{(b)(4)} in the final drug product formulation using an validated analytical method and propose a release specification to adequately control \textsuperscript{(b)(4)} in the drug product.

PMR/PMC Schedule Milestones:
- Final Protocol Submission: N/A
- Study/Trial Completion: 12/2016
- Final Report Submission: 02/2017
- Other: MM/DD/YYYY

36. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The levels \textsuperscript{(b)(4)} in a drug product formulation have only recently been regulated specifically \textsuperscript{(b)(4)}. As such, this assessment is being allowed to be completed post-marketing.

37. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study will characterize the levels \textsuperscript{(b)(4)} in the final drug product formulation. Currently, the \textsuperscript{(b)(4)} levels are specified for several of the excipients individually which carry the greatest risk. A study to characterize the levels \textsuperscript{(b)(4)} in the final drug product will ensure the \textsuperscript{(b)(4)} levels remain within current guidelines and will take into consideration all of the excipients in the drug product formulation. The standard requirements have only recently been changed and the Sponsor will have to develop a validated analytical method to measure \textsuperscript{(b)(4)} in the final drug product formulation in order to complete this study.
38. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - [ ] Analysis of spontaneous postmarketing adverse events?
    - *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?
    - *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

39. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   *This is an analytical chemistry study that entails development of methodology to characterize the potential levels \( b \) in the final drug product formulation. Once completed, using a validated analytical method, proposals for specifications must be submitted based on a toxicological risk assessment.*

   **Required**
   - [ ] Observational pharmacoepidemiologic study
   - [ ] Registry studies
   - [ ] Primary safety study or clinical trial
   - [ ] Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
   - [ ] Thorough Q-T clinical trial
   - [ ] Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

40. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________

(signature line for BLAs)
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

JUDITH A RACOOSIN
04/26/2016
## 505(b)(2) ASSESSMENT

### Application Information

<table>
<thead>
<tr>
<th>NDA # 208090</th>
<th>NDA Supplement #: S-</th>
<th>Efficacy Supplement Type SE-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprietary Name: Xtampza ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established/Proper Name: oxycodone extended-release</td>
<td></td>
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<tr>
<td>Dosage Form: capsules</td>
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<tr>
<td>Strengths: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg</td>
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<tr>
<td>Applicant: Collegium Pharmaceutical</td>
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<td></td>
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<tr>
<td>Date of Receipt: December 12, 2014</td>
<td></td>
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<tr>
<td>PDUFA Goal Date: October 12, 2015</td>
<td>Action Goal Date (if different): October 9, 2015</td>
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<tr>
<td>RPM: Ayanna Augustus, PhD, RAC</td>
<td></td>
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<tr>
<td>Proposed Indication(s): management of pain severe enough to require daily, around-the-clock, long-term opioid tx and for which alternative options are inadequate</td>
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</tbody>
</table>

### GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

   YES ☐ NO ☒

   If “YES” contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.
INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. (If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)

<table>
<thead>
<tr>
<th>Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)</th>
<th>Information relied-upon (e.g., specific sections of the application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>published literature</td>
<td>Nonclinical toxicology—safety of excipients</td>
</tr>
<tr>
<td>NDA 22272/OxyContin</td>
<td>FDA’s previous finding of safety and effectiveness: indication, Dosage and Administration, contraindications, Warnings, Adverse Reactions, Drug Interactions, Use in Specific Populations, Overdose, Clinical Pharmacology, Nonclinical Toxicology.</td>
</tr>
</tbody>
</table>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature.

- The sponsor conducted two bioavailability studies, CP-OXYDET-15 and CP-OXYDET-18, between the proposed product and OxyContin. CP-OXYDET-15 is a single dose relative BA study between the proposed product and OxyContin; CP-OXYDET-18 is a multiple dose relative BA study between the proposed product and OxyContin.
- Safety assessment of excipients is based, in part, on published papers of toxicity studies of several components of beeswax and carnauba wax, safety of myristic acid and hypromellose. (a) [a]

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application cannot be approved as labeled without the published literature)?

YES ☒ NO ☐

If “NO,” proceed to question #5.
(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) listed drug product?

YES ☐ NO ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☒

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

<table>
<thead>
<tr>
<th>RELIANCE ON LISTED DRUG(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.</td>
</tr>
</tbody>
</table>

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application rely on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If “NO,” proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(#s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

<table>
<thead>
<tr>
<th>Name of Listed Drug</th>
<th>NDA #</th>
<th>Did applicant specify reliance on the product? (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>22272</td>
<td>yes</td>
</tr>
</tbody>
</table>

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer “N/A”.

If “NO”, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

   YES ☐ NO ☒

   If “YES”, please list which drug(s).

   Name of drug(s) approved in a 505(b)(2) application:
b) Approved by the DESI process?  
YES ☐  NO ☒  
If “YES”, please list which drug(s).
Name of drug(s) approved via the DESI process:

If “YES”, please list which drug(s).
Name of drug(s) described in a final OTC drug monograph:

c) Described in a final OTC drug monograph?  
YES ☐  NO ☒  
If “YES”, please list which drug(s).

d) Discontinued from marketing?  
YES ☐  NO ☒  
If “YES”, please list which drug(s) and answer question d) i. below.  
If “NO”, proceed to question #9.
Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?  
YES ☐  NO ☒  
(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Abuse deterrent properties; extended release microspheres

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive
ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

*Note* that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

**YES** □ **NO** ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

**YES** □ **NO** ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A □ **YES** □ **NO** ☒

If this application relies only on non product-specific published literature, answer “**N/A**” If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note* that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

**YES** ☒ **NO** □

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

**YES** ☒ **NO** □
(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

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<tr>
<th></th>
<th>N/A</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

If this application relies only on non product-specific published literature, answer “N/A”
If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.
If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

- NDAs: 22272, 200534, 200535, 201194, 202080, 21011
- ANDAs: 202773, 20310, 203823, 203107, 204752, 204979, 204092, 204085, 204603, 203208, 20403, 206456, 76636, 202160, 91393, 91313, 90895, 76758, 77290, 91490, 90659, 77712, 21011

### PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6488963, 7674799, 7674800, 7683072, 7776314, 8114383, 8309060, 8337888, 8808741, 8894987, 8894988, 9060976 and 9073933

- No patents listed  
  | proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

- YES  
  - NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):  

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):  

Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*


☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6488963, 7674799, 7674800, 7683072, 7776314, 8114383, 8309060, 8337888, 8808741, 8894987, 8894988, 9060976 and 9073933

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  

   YES ☑ NO ☐  

   *If “NO”, please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  

   YES ☑ NO ☐  

   *If “NO”, please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):
Date(s): **February 12 and 13, September 24, 2015**

*Note*, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided.

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note* that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval
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

Reference ID: 3918344
Memorandum

Date: April 8, 2016

To: Ayanna Augustus, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208090
Xtampza ER (oxycodone extended-release) Capsules
Professional Labeling Review

As requested in DAAAP’s consult dated March 7, 2016, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for Xtampza ER Capsules. The substantially complete prescribing information was provided to OPDP on March 7, 2016, via email by Ayanna Augustus with the file name "\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 208090 (Oxycodone DETERx Collegium)\Request for Final Approval\Labeling".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made comments on pages 7, 8, 10 and 29.

OPDP has no comments on the carton and container labeling submitted February 26, 2016.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

Reference ID: 3914409
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/s/

-----------------------------------------------
KOUNG U LEE
04/08/2016
To: Joan Blair, Health Communications Analyst, DRISK

From: Koung Lee, Regulatory Review Officer, OPDP

CC: Jessica Fox, Regulatory Review Officer, OPDP
    Vaishali Jarral, Regulatory Project Manager, OSE
    Kimberly Lehrfeld, Team Leader, DRISK
    Jamie Wilkins-Parker, Senior Risk Management Analyst, DRISK
    CDER-OPDP-RPM
    Olga Salis, Regulatory Project Manager, OPDP

Date: March 14, 2016

Re: ER/LA Opioid SSS Risk Evaluation and Mitigation Strategies (REMS) Modification

Materials Reviewed

OPDP has reviewed the proposed modifications to the SSS REMS materials for ER/LA opioid products.

The version of the draft REMS material used in this review, titled, “Xtampza. Risk-evaluation-and-mitigation-strategy.FDA Review. March 2016.doc”, was provided by DRISK via email (Joan Blair, Health Communication Analyst) on Thursday, March 10, 2016, and is attached to the end of this review.

OPDP offers the following comments on the draft REMS materials for the ER/LA REMS.

General Comment

Please remind the sponsors that REMS materials are not appropriate for use in a promotional manner.
REMS Materials

OPDP does not object to the modifications made to the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.

We have no additional comments on the proposed REMS materials at this time.

Thank you for your consult.

Enclosure:
REMS Materials
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/s/

KOUNG U LEE
03/23/2016
PATIENT LABELING REVIEW

Date: March 18, 2016

To: Sharon Hertz, MD
    Acting Director
    Division of Anesthesia, Analgesia, and Addiction Products (DAAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
          Associate Director for Patient Labeling
          Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
       Patient Labeling Reviewer
       Division of Medical Policy Programs (DMPP)

Subject: DMPP review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): XTAMPZA ER (oxycodone) extended-release capsules, for oral use, CII
Dosage Form and Route: NDA 208090
Applicant: Collegium Pharmaceutical, Inc.
1 INTRODUCTION

On February 26, 2016, Collegium Pharmaceutical, Inc. submitted for the Agency’s review a Request for Final Approval for their tentatively approved New Drug Application (NDA) 208090 for XTAMPZA ER (oxycodone) extended-release capsules. XTAMPZA ER (oxycodone) extended-release capsules received tentative approval on November 6, 2015, which was later re-issued on December 8, 2015. XTAMPZA ER (oxycodone) is indicated 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.

On March 8, 2016, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for XTAMPZA ER (oxycodone) extended-release capsules.

2 MATERIAL REVIEWED

- Draft XTAMPZA ER (oxycodone) extended-release capsules MG and IFU received on February 26, 2016, and received by DMPP on March 7, 2016.
- Draft XTAMPZA ER (oxycodone) extended-release capsules Prescribing Information (PI) received on February 26, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on March 7, 2016.

3 CONCLUSIONS

We find the Applicant’s proposed MG and IFU acceptable with our minor formatting changes.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.
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/s/

MORGAN A WALKER
03/18/2016

BARBARA A FULLER
03/18/2016
Date of This Memorandum: March 7, 2016
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208090
Product Name and Strength: Xtampza ER (oxycodone) Extended-release capsules
9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Submission Date: February 26, 2016
Applicant/Sponsor Name: Collegium Pharmaceuticals
OSE RCM #: 2016-518
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO
The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels for Xtampza ER (Appendix A) to determine if it is acceptable from a medication error perspective. We found the container labels acceptable in a previous review.\(^1\) As part of their Class I resubmission, Collegium submitted new container labels which include the addition of the NDC numbers to the top of the labels and changes to the strength presentation colors.

\(^1\) Schlick J. Label and Labeling Review Memo for Xtampza ER (NDA 208090). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 6. 4 p. OSE RCM No.: 2014-2548-1.
2 CONCLUSION
The revised container labels for Xtampza ER is acceptable from a medication error perspective. We have no further recommendations at this time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES H SCHLICK
03/07/2016

BRENDA V BORDERS-HEMPHILL
03/08/2016
Memorandum to File

From: Jay Sitlani, ORP/CDER

Date: October 30, 2015

Re: NDA 208090, Xtampza ER (oxycodone extended-release) Capsules: status of 30-month stay of approval

This memorandum was prepared in conjunction with the Office of Chief Counsel to address the status of the 30-month stay of approval for NDA 208090, Xtampza ER (oxycodone extended-release) Capsules.

Background

At issue is whether dismissal of a patent infringement action for lack of personal jurisdiction, which is later vacated\(^1\) and transferred to another venue, terminates a 30-month stay of approval of a 505(b)(2) application. Collegium Pharmaceutical, Inc. (“Collegium”), sponsor of NDA 208090, argues that the 30-month stay for this drug was terminated. Purdue Pharma L.P. (“Purdue”) argues that the stay remains in effect. For the reasons described below, we conclude that the 30-month stay currently is in effect.

Statutory and Regulatory Background

Under section 505(c)(3)(C) of the Federal Food, Drug, and Cosmetic Act (“FD&C Act”), if a 505(b)(2) applicant makes a certification under section 505(b)(2)(A)(iv) and provides notice as described in section 505(b)(3), and within 45 days an “action is brought for infringement of the patent that is the subject of the certification,” a 30-month stay of approval results. The statute provides specific circumstances, relating to different types of court decisions, which terminate the stay. The relevant language states:

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\(^1\) As described below, supra note 17, the relevant order is not expressly characterized as vacating the earlier dismissal order.
the approval [of the (b)(2) application] may be made effective upon the expiration of the thirty-month period\(^2\) beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271 (e)(4)(A) of title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

\(^2\) In certain circumstances for drugs subject to 5-year statutory exclusivity, not applicable here, a 7 ½ year period applies. See FD&C Act § 505(c)(3)(E)(ii); 21 C.F.R. 314.107(b)(3)(i)(B).
In such an action, each of the parties shall reasonably cooperate in expediting the action.

Neither the above-quoted statutory text nor the implementing regulation at 21 C.F.R. 314.107 express a circumstance in which the infringement case is dismissed without substantively addressing the patent claims and where that dismissal was subsequently vacated and the court case reinstated. In the preamble to the proposed “Abbreviated New Drug Applications and 505(b)(2) Applications” regulation (“MMA proposed rule”), FDA recently stated:

The MMA’s amendments to section 505(c)(3)(C)(i), (c)(3)(C)(ii), (j)(5)(B)(iii)(I), and (j)(5)(B)(iii)(II) of the FD&C Act clarify the timing of approval of a 505(b)(2) application or ANDA, respectively, in relation to a settlement order or consent decree stating that the patent that is the subject of the paragraph IV certification is invalid or not infringed. However, the statute does not address whether a 30-month stay may be terminated and a 505(b)(2) application or ANDA approved if the court enters an order of dismissal without a finding of patent infringement—a scenario that FDA encounters frequently. We are proposing to add § 314.107(b)(3)(viii) to codify FDA’s policy that court entry of an order of dismissal, with or without prejudice, of patent infringement litigation that was timely initiated in response to notice of a paragraph IV certification will terminate the 30-month period (or 7½ years where applicable) if such order does not state a finding of patent infringement. It is appropriate that a 30-month stay terminates under these circumstances because the statutory purpose of the stay is to allow time for claims of patent infringement to be litigated prior to approval of the potentially infringing drug product. If the patent owner or exclusive patent licensee dismisses the patent infringement action on terms that the court considers proper (see Fed. R. Civ. P. Rule 41(a)(2)), then there should be no further delay of approval of a 505(b)(2) application or ANDA otherwise eligible for approval.4

Factual Background

In this case, Collegium has filed a 505(b)(2) application for an extended release oxycodone product that relies upon FDA’s finding of safety and/or effectiveness for Purdue’s OxyContin (NDA 022272). Collegium sent notice of its paragraph IV certification to Purdue, and Purdue initiated two infringement actions within 45 days, giving rise to a 30-month stay of approval under section 505(c)(3)(C) of the FD&C Act.

The chart below summarizes the relevant events pertaining to these actions:

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3 FDA has proposed revisions to 21 C.F.R. 314.107 to reflect the revisions to section 505(c)(3)(C) made by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (“MMA”), but the regulation has not yet been amended.

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<th>Action</th>
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| 3/24/15    | Purdue files an infringement action in the U.S. District Court for the District of Delaware ("D. Del.") (15-cv-00260).  
| 4/6/15     | Collegium moves to dismiss D. Del. action for lack of personal jurisdiction; seeks transfer to the U.S. District Court for the Southern District of New York ("S.D.N.Y.").  
| 8/6/15     | D. Del. dismisses action for lack of personal jurisdiction.  
| 8/6/15     | Collegium files declaratory action in S.D.N.Y. seeking a determination of non-infringement and invalidity (15-cv-06179).  
| 8/7/15     | Purdue files motion for "re-argument" in D. Del to vacate dismissal.  
| 10/7/15    | D. Del. issues an order to vacate its dismissal and transfers venue of the action to D. Mass.  

The Delaware district court’s August 6, 2015 order granted in part and denied in part Collegium’s motion to dismiss for lack of personal jurisdiction, or in the alternative, transfer venue to the Southern District of New York. The memorandum opinion explained that the court lacked personal jurisdiction over Collegium and the case should be dismissed under Federal Rule of Civil Procedure 12(b)(2). The court denied Collegium’s request to transfer venue to the Southern District of New York, reasoning that personal jurisdiction over Collegium should exist in Massachusetts, and Purdue could pursue its “protective lawsuit” filed in that district. The court did not appear to be aware that Purdue had, approximately two weeks earlier, voluntarily dismissed the Massachusetts case. Neither party asserts that the decision reached the merits of the infringement claims asserted in Purdue’s complaint.

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5 Case 15-cv-00260, Docket No. 1.
6 Case 15-cv-11294, Docket No. 1.
7 Case 15-cv-00260, Docket Nos. 8, 9.
9 Case 15-cv-00260, Docket No. 29, 30.
10 Case 15-cv-13099, Docket No. 1.
12 Case 15-cv-00260, Docket No. 38.
13 Case 15-cv-00260, Docket No. 29, at 4-11.
14 Id. at 11-12.
15 Counsel for Collegium argues, in a footnote, that Purdue has “admitted” that another district court in separate litigation found that the listed patents at issue were invalid, and this concession should serve to terminate the 30-month stay. See Letter from Kurt R. Karst, to Elizabeth Dickinson & Kim Dettelbach (Oct. 9, 2015), at 2-3, n.1 ("Oct. 9 Karst Letter"). Even if Collegium’s characterization is valid, we interpret section 505(c)(3)(C)(i) to terminate a stay only when the court decision is in the action that gave rise to the stay in the first place. The reference to “the district court” in clause (i) is read most naturally to refer to the court adjudicating the action described immediately above in paragraph (C).
Purdue immediately filed a motion for reargument, in which it argued that Collegium had consented to personal jurisdiction in Delaware. In response to Purdue’s motion for reargument, the Delaware district court issued a memorandum order on October 7, 2015 vacating the August 6, 2015 order. The order explains that although Collegium stated in oral argument that “it would consent to jurisdiction in Delaware if necessary to avoid starting from scratch in Massachusetts,” Collegium “did not formally consent to jurisdiction.” The court ordered, however, “that rather than dismissal, the case shall be transferred to the District of Massachusetts, which was the intended destination in the first instance.”

The parties have submitted correspondence providing their characterization of the relevant facts and legal theories in support of their positions. On August 7, 2015, Collegium submitted a letter to FDA stating that dismissal of the Massachusetts and Delaware actions terminated the 30-month stay. On October 6, Peter Mathers, counsel for Purdue, submitted a letter to FDA’s Office of Chief Counsel arguing that, to date, no action had occurred that would terminate the 30-month stay. Purdue argued that there was “no entry of a settlement order, consent decree or court judgment finding that the patents that underlay that action are invalid or not infringed.” Purdue also argued that the “Delaware action continues to be litigated.”

On October 7, 2015, Kurt Karst, counsel for Collegium, submitted a letter to FDA’s Office of Chief Counsel arguing that both patent infringement actions filed by Purdue within the statutory 45-day period “have been dismissed by the courts, terminating any 30-month litigation stay.” Collegium argued that “[w]here no timely filed patent infringement action remains pending, there can be no 30-month stay.” Collegium supported this statement by referencing the MMA proposed rule passage described above. Later, on October 7, counsel for Purdue emailed the October 7, 2015 order to FDA’s Office of Chief Counsel and asserted that “[b]ased on today’s order, the original complaint, and the infringement claims raised therein, continue to be litigated and the 30-month stay continues in effect.”

On October 9, 2015, Kurt Karst, counsel for Collegium, submitted a second letter to FDA’s Office of Chief Counsel. The letter asserted that “the controlling statute, FDA precedent, and FDA guidance all dictate that once a suit is dismissed for any reason, the 30-month litigation stay terminates and is not revived by a subsequent reversal or vacatur.” Collegium argued that the

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16 Case 15-cv-00260, Docket No. 38, at 3. The order explains that a “motion for reargument” is the “functional equivalent” of a motion to alter or amend judgment under Fed. R. Civ. P. 59(e). Id. at 1.
17 Id. at 3. We note that the order does not expressly state that the August 6, 2015 order was “vacated.” Both parties characterize the October 7 order as vacating or “apparent[ly]” vacating the August 6, 2015 order, however, and we will adopt that terminology here. See Oct. 9 Karst Letter at 2; Email from Peter Mathers, to Elizabeth Dickinson & Kim Dettelbach (October 7, 2015) (“Oct. 7 Mathers Email”).
18 Letter from John F. Weet, PhD, to Sharon Hertz, M.D., FDA, Center for Drug Evaluation and Research (Aug. 7, 2015).
19 Letter from Peter Mathers to Elizabeth Dickinson & Kim Dettelbach, FDA, Office of Chief Counsel (Oct. 6, 2015).
21 Id. at 2-3.
22 Oct. 7 Mathers Email.
23 Oct. 9 Karst Letter at 1.
result is “compelled by the statute’s plain language,” citing to section 505(c)(3)(C)(i).\textsuperscript{24} Collegium argued that FDA has previously taken the view that “vacatur of a judgment terminating a 30-month stay . . . by itself has no effect on FDA’s ability to approve an application.”\textsuperscript{25} Collegium also cited to FDA’s approval of a 505(b)(2) application for an oxaliplatin injection product and the U.S. District Court for the District of Columbia’s decision rejecting a challenge to the approval.\textsuperscript{26}

**Discussion**

The precise issue here is whether the Delaware district court’s dismissal of the infringement action for lack of personal jurisdiction terminated the 30-month stay, even though the district court later vacated that decision and the patent issues continue to be litigated. We conclude that the stay remains in effect.

As described in the MMA proposed rule, “the statute does not address whether a 30-month stay may be terminated and a 505(b)(2) application or ANDA approved if the court enters an order of dismissal without a finding of patent infringement.”\textsuperscript{27} FDA’s general policy has been that a court entry of an order of dismissal, with or without prejudice, of patent infringement litigation that was timely initiated in response to notice of a paragraph IV certification will terminate the 30-month period if the order does not state a finding of patent infringement. In the proposed MMA rule, FDA explained that “[i]t is appropriate that a 30-month stay terminates under these circumstances because the statutory purpose of the stay is to allow time for claims of patent infringement to be litigated prior to approval.”\textsuperscript{28}

To our knowledge, FDA has not addressed a case in which the order of dismissal (without a finding of patent infringement) was vacated, and the infringement action giving rise to the 30-month stay remains pending at the time FDA is ready to act on the 505(b)(2) application. Under the unique and specific facts at issue here,\textsuperscript{29} we have determined that the 30-month stay remains in effect. The purpose of the above-described general policy is to interpret the statutory ambiguity in section 505(c)(3)(C) in a manner that furthers Congress’ intent – to allow the parties time to litigate claims of patent infringement. As described in the MMA proposed rule, in the common example where the patent owner or exclusive patent licensee dismisses the patent infringement action voluntarily on terms that the court considers proper, and the litigation thereby ends, Congress’ intent is served by terminating the stay. In this case, because the Delaware district court ultimately determined that its dismissal was not proper and the order of

\begin{footnotesize}
\begin{enumerate}
\item Id. at 2.
\item Id. at 3 (citing FDA, Guidance for Industry Court Decisions, ANDA Approvals, and 180-day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act (Mar. 2000) (“Court Decision Guidance”).
\item 80 Fed. Reg. at 6864.
\item Id.
\item We note that FDA evaluates the status of the 30-month stay only at the time a 505(b)(2) application is otherwise ready for approval.
\end{enumerate}
\end{footnotesize}
dismissal was vacated, and the original infringement action giving rise to the stay remains pending, Congress’ intent is served by considering the stay to be in effect. Collegium argues in its October 9 letter that the outcome of this matter is dictated by the plain language of section 505(c)(3)(C)(i), FDA’s approach described in the Court Decision Guidance, FDA’s approval of the above-referenced 505(b)(2) application for oxaliplatin, and the district court’s decision in *Sanofi-Aventis v. FDA*. We disagree. Collegium does not point to any evidence that the August 6, 2015 decision reached the substance of Purdue’s patent infringement claims. Upon reviewing the memorandum opinion, we conclude that the court addressed only the jurisdictional and procedural issues of personal jurisdiction and venue. Thus, we do not believe that the order and opinion constitute the type of substantive decisions described in section 505(c)(3)(C)(i), and therefore this matter is not governed by the plain language of section 505(c)(3)(C)(i). Accordingly, Collegium misplaces its reliance on the Court Decision Guidance, FDA’s approval of oxaliplatin, and the *Sanofi-Aventis* case, all of which are premised on a substantive court decision of patent invalidity or infringement. 30 Instead, as described above, we believe that the statute does not address the effect of an order of dismissal without a finding of patent infringement. Under the unique facts of this matter, where the court dismissed the relevant action for lack of personal jurisdiction and then vacated that decision before the time FDA is ready to act on the 505(b)(2) application, we believe that the 30-month stay should remain in effect for the reasons described above.

**Conclusion**

For the reasons described above, we conclude that the 30-month stay currently is in effect for NDA 208090 and FDA cannot grant final approval to this application at this time.

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30 *See Sanofi-Aventis*, 643 F. Supp. 2d at 86 (interpreting FD&C Act § 505(c)(3)(C)(i)(I)); Shimer Memorandum, at 2-5 (interpreting FD&C Act § 505(j)(5)(B)(iii)(I)). The Court Decision guidance concerned the pre-MMA version of section 505(j)(5)(B)(iii)(I), which stated “if before the expiration of [the 30-month period] the court decides that such patent is invalid or not infringed, the approval may be made effective on the date of the court decision.”
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/s/

AYANNA S AUGUSTUS
11/06/2015

SHARON H HERTZ
11/06/2015
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 6, 2015
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208090
Product Name and Strength: Xtampza ER (oxycodone) Extended-release Capsules 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Submission Date: October 5, 2015
Applicant/Sponsor Name: Collegium Pharmaceuticals
OSE RCM #: 2014-2548-1
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO
The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels for Xtampza ER (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.1

2 CONCLUSION
The revised container labels for Xtampza ER is acceptable from a medication error perspective. We have no further recommendations at this time.

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

/s/

JAMES H SCHLICK
10/06/2015

BRENDA V BORDERS-HEMPHILL
10/07/2015
Division of Pediatric and Maternal Health Memorandum

Date: October 1, 2015       Date consulted: January 7, 2015

From: Miriam Dinatale, DO, Medical Officer, Maternal Health
       Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
         Division of Pediatric and Maternal Health

         Lynne P. Yao, MD, OND, Division Director
         Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: Xstampza ER (oxycodone extended release) capsules

NDA: 208090

Applicant: Collegium Pharmaceutial, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate

Materials Reviewed:
- DPMH consult request dated January 7, 2015, DARRTS Reference ID 3683698
- Sponsor’s submitted background package for NDA 208090, Xstampza ER
- DPMH review for Xartemis (NDA 204031). Leyla Sahin, MD. October 28, 2013, DARRTS Reference ID 3397647
- DPMH review for Targiniq (NDA 205777). Miriam Dinatale, DO. June 20, 2014, DARRTS Reference ID 3526040
Consult Question:
DAAAP requests DPMH assistance with pregnancy and lactation labeling for this NDA

INTRODUCTION
On December 12, 2014, Collegium Pharmaceutical, Inc., submitted a 505 (b)(2) New Drug Application (NDA) for Xtampza ER (oxycodone extended release) capsules (NDA 208090) 22496 for the proposed indication of analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. In addition to relying on the FDA’s previous findings of safety and efficacy for the Referenced Listed Drug (RLD) OxyContin, NDA 22272, the applicant also submitted results of a Phase 3 trial using Xtampza ER to support the safety and efficacy of their product.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 7, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Xtampza labeling with conversion to Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND
Oxycodone and Mechanism of Action
Oxycodone is a semisynthetic opioid analgesic with affinity for mu, kappa, and delta receptors in the brain, spinal cord and peripheral organs. Opioid medications may be needed during pregnancy to manage severe pain associated with many conditions, including both acute and chronic medical conditions and surgical procedures. Recent studies show that the prevalence of opioid use among pregnant women ranges from 2% to 20%, and usage of opioids in pregnancy has been increasing.

Opioid Analgesic Drug Products’ Class Labeling
On September 10, 2013, the FDA implemented safety labeling changes related to neonatal opioid withdrawal syndrome (NOWS) for extended-release/long-acting (ER/LA) opioid analgesics. The Office of Regulatory Policy received a citizen petition from the National Advocates for Pregnant Women on October 17, 2013. On April 11, 2014, DPMH completed a review in response to the citizen’s petition and discussed recommended labeling for NOWS. Newly required class labeling for opioid analgesic drug products (applies to Schedule II controlled substances with extended release or long acting (ER/LA) formulations) has been issued. As part of the class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression (that can lead to overdose and death) and NOWS (which may be life threatening in neonates whose mothers required prolonged opioid

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3 Co-Primary Authors Leyla Sahin, MD, Amy Taylor, MD, MHS. Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS Reference ID: 3488324
therapy while pregnant). In addition to the boxed warnings, there is class labeling in several sections and sub-sections.4

**Pregnancy and Nursing Mothers Labeling**
On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”5 also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule6 format to include information about the risks and benefits of using these products during pregnancy and lactation.

**REVIEW OF DATA**

**Nonclinical Information**
No embryonic developmental toxicity studies or pre- or postnatal development studies were conducted for NDA 208090. The applicant relied on FDA’s previous nonclinical findings from OxyContin, NDA 022272. In animal reproduction studies, there was no evidence of fetal harm when oxycodone was orally administered to rats and rabbits at 0.5 and 15 times the adult human dose of 160mg/day, respectively, during the period of organogenesis. In a pre- and postnatal toxicity study, when oxycodone was administered orally to rats at doses within the dosing range of humans, there was transiently decreased pup body weight during lactation and the early post-weaning period at a dose equivalent to 0.4-times an adult dose of 160 mg/day.

The applicant submitted one published article on a pre- and postnatal development study. The authors (Davis, et al.) noted that offspring of rats administered oxycodone, at clinically relevant doses and below, from breeding through parturition were found to have neurobehavioral effects that included altered stress responses, hyperactivity, increased anxiety and altered learning and behavior.7

The reader is referred to the Nonclinical Review by Grace Lee, Ph.D. for further details.8

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4 Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).
5 Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).
6 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
7 Davis, et al. Prenatal oxycodone exposure impairs spatial learning and/or memory in rats. Behav Brain Res. 212: 27-34.
Oxycodone and Pregnancy
The applicant did not conduct studies with Xtampza ER in pregnant women. There were two pregnancies that occurred during the double-blind maintenance phase of study CP-OXYDET-08\(^9\) (Phase 3) study, but both women were assigned to the placebo arm. One subject had a confirmed molar pregnancy; the other subject was lost to follow-up, and the outcome of the pregnancy is unknown. There were no pregnancies that occurred in patients taking the study drug.\(^{10}\) See Appendix B for further details on the two reported pregnancies.

Overall, the cumulative data on opioid exposure during pregnancy and the incidence of congenital malformations are very limited. The data on opioid exposure during pregnancy were reviewed by DPMH in 2013, and the reader is referred to the DPMH Review by Leyla Sahin, MD for further details. There were three published case-control studies that demonstrated statistically significant associations between opioid exposure in the first trimester of pregnancy and congenital malformations\(^{11,12,13}\) and two published studies that did not show an increase in congenital malformations.\(^{14,15}\)

Additionally, in an FDA Drug Safety Communication issued on January 9, 2015, DAAAP, the Office of Surveillance and Epidemiology (OSE) and DPMH reviewed opioids, including oxycodone, hydrocodone, hydromorphone, morphine and codeine, and evaluated the risk of birth defects of the brain, spine or spinal cord in infants born to women who took these products during the first trimester of pregnancy. FDA found that all of the studies reviewed have limitations in their designs; therefore, it is not possible to draw any conclusions regarding the risks of malformations following exposure to opioids during pregnancy.\(^{16}\)

Oxycodone and Neonatal Opioid Withdrawal Syndrome
Overall, infants of patients who took opioids during pregnancy are at risk for NOWS, which may be life-threatening if NOWS is not recognized early and appropriate treatment initiated. Infants of mothers who are using opioids throughout pregnancy should be carefully monitored for signs of withdrawal after birth. The reader is referred to the FDA implemented safety labeling changes related to NOWS for ER/LA opioid analgesics (September 10, 2013)\(^{17}\)

\(^9\) OXYDET-08: Phase 3, randomized withdrawal, double-blind, placebo-controlled multicenter study to demonstrate the safety and efficacy of Xtampza ER compared with placebo in subjects with moderate-to-severe chronic lower back pain.

\(^{10}\) Collegium Pharmaceutical, Inc. Clinical Study Report: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Efficacy Study of Oxycodone DETERx versus placebo in Opioid-Experience and Opioid-Naïve Subjects with Moderate-to-Severe Chronic Low Back Pain. 11/12/2014.


\(^{17}\) Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February
and the DPMH review by Leyla Sahin, MD and Amy Taylor, MD, MHS that discusses the response to the Citizen Petition regarding NOWS labeling change for further details.\textsuperscript{18}

Current oxycodone labeling recommends that oxycodone should be used during pregnancy only if the potential benefit justifies the risk to the fetus. DPMH review found no new safety information that needs to be added to labeling. DPMH recommends that based on animal data, pregnant women should be advised of the potential risk of neurobehavioral effects to a fetus.

**Oxycodone and Lactation**

The Drugs and Lactation Database (LactMed)\textsuperscript{19} was searched for available lactation data on the use of oxycodone. Overall, LactMed notes that the “maternal use of narcotics during breastfeeding can result in infant drowsiness, central nervous system depression and even death.” In the 2013 Clinical Report on the Transfer of Drugs and Therapeutics into Human Breast Milk, the American Academy of Pediatrics (AAP) noted that relatively high amounts of oxycodone are present in human milk, and therapeutic concentrations of oxycodone have been detected in the plasma of a nursing infant. Since CNS depression was noted in 20\% of infants exposed to oxycodone during breastfeeding, the AAP recommends that the use of oxycodone be discouraged in a breastfeeding mother.\textsuperscript{20}

Current oxycodone labeling recommends that oxycodone not be used in a breastfeeding mother because of the possibility of sedation and respiratory depression in the infant.\textsuperscript{21} DPMH review found no new safety information that needs to be added to labeling. DPMH recommends that breastfeeding is not recommended during treatment with Xtampza ER, which is consistent with lactation recommendations for other ER/LA opioids. The reader is referred to previous DPMH reviews by Leyla Sahin, MD and Miriam Dinatale, DO for a complete review of published literature related to oxycodone and lactation.\textsuperscript{22,23,24}

\textsuperscript{18} Leyla Sahin, MD, Amy Taylor, MD, MHS. Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS Reference ID: 3488324
\textsuperscript{19} http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
\textsuperscript{20} Sachs HC. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on selected topics. Pediatrics 2013; 132(3).
\textsuperscript{21} Oxycodone HCl, NDA 22272. Drugs@FDA. Nursing Mothers section of labeling. Accessed 9/15/2015.
\textsuperscript{22} DPMH review for Xartemis (NDA 204031). Leyla Sahin, MD. October 28, 2013, DARRTS Reference ID 3397647
\textsuperscript{23} DPMH review for Targiniq (NDA 205777). Miriam Dinatale, DO. June 20, 2014, DARRTS Reference ID 3526040
\textsuperscript{24} DPMH review for Troxyca ER (NDA 207621). Miriam Dinatale, DO. September 22, 2015. DARRTS Reference ID 3825358
Oxycodone and Females and Males of Reproductive Potential
DPMH conducted a review of published literature in PubMed regarding the effects of oxycodone on fertility. There were no published articles using the search terms “oxycodone” and “infertility.” There was one relevant published article using the search terms “oxycodone” and “hypogonadism” that was reviewed by DPMH in a prior review. Overall, there is limited information about oxycodone and infertility, and DPMH does not recommend labeling regarding infertility at this time.

CONCLUSIONS
Xtampza ER labeling has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with oxycodone use in pregnant or lactating women. DPMH has the following recommendations for Xtampza ER labeling:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of Xtampza ER labeling was formatted in the PLLR format to include “Risk Summary,” “Clinical Considerations,” and “Data” subsections.

- **Lactation, Section 8.2**
  - The “Lactation” subsection of Xtampza ER labeling was formatted in the PLLR format to include the “Risk Summary” and “Clinical Considerations” subsections.

- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of Xtampza ER labeling was updated to correspond with changes made to sections 5.3, 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS FOR XTAMPZA ER LABELING
DPMH revised subsections 8.1, 8.2 and 17 in Xtampza ER labeling for compliance with the PLLR (see below). The boxed warning and section 5.3 was left unchanged. DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling.)

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25 DPMH review for Troxyca ER (NDA 207621). Miriam Dinatale, DO. September 22, 2015. DARRTS Reference ID 3825358


HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME
Prolonged use of XAMPZA ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3)

---USE IN SPECIFIC POPULATIONS---
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

FULL PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME
Prolonged maternal use of XAMPZA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].

5  WARNINGS AND PRECAUTIONS
5.3 Neonatal Opioid Withdrawal Syndrome
Prolonged use of XAMPZA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid-withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts.

8  USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. There are no available data with XAMPZA ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryofetal toxicity when oxycodone hydrochloride was orally administered to rats and rabbits during the period of...
organogenesis at doses 0.5 and 15 times the adult human dose of 160mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was administered orally to rats at doses within the dosing range of humans, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to approximately 0.4-times an adult dose of 160 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Fetal/Neonatal adverse reactions
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, and manage accordingly [see Warnings and Precautions (5.3)].

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. XTAMPZA ER is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including XTAMPZA ER, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Data
Animal data
Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 15 times an adult human dose of 160 mg/day, respectively on a mg/m² basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by dams given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m² basis). However, body weight of these pups recovered. In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from
Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.1-times an adult human oral dose of 160 mg/day on a mg/m² basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; equivalent to an adult human oral dose of 160 mg/day on a mg/m² basis).

8.2 Lactation
Risk Summary
Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfeeding infants for potential adverse reactions. Lactation studies have not been conducted with extended-release oxycodone, including XTPAZA ER, and no information is available on the effects of the drug on the breastfeeding infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfeeding infant, advise patients that breastfeeding is not recommended during treatment with XTPAZA ER.

Clinical Considerations
Infants exposed to XTPAZA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

17 PATIENT COUNSELING INFORMATION
Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of XTPAZA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see Warnings and Precautions (5.3), see Use in Specific Populations (8.1)].

Advise that XTPAZA ER can cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise patients that breastfeeding is not recommended during treatment with XTPAZA ER [see Use in Specific Populations (8.2)].

Medication Guide
Tell your healthcare provider if you are:
- pregnant or planning to become pregnant. Prolonged use of XTPAZA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- breastfeeding. Not recommended.

Reference ID: 3828060
APPENDIX A - Applicant’s Proposed Pregnancy and Nursing Mothers Labeling

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

Reference ID: 3828060
APPENDIX B: Pregnancies occurring during the Double-Blind Maintenance Phase of Study CP-OXYDET

1.) **Subject 115-1023:** A 22-year-old female was enrolled in study CP-OXYDET-08 on March 5, 2013 and received her first dose of Oxycodone DETERx (Xtampza ER), 10mg twice a day, during the titration phase of the study and was titrated up to 20mg twice a day. On April 4, 2013, the subject was randomized to the Double-blind Maintenance Phase of the study and received placebo. The patient had a positive pregnancy test on May 15, 2013 and was discontinued from the study. There is no mention of the patient’s last menstrual period or how far along she was in pregnancy. The subject was diagnosed with a complete molar pregnancy on July 2, 2013 and underwent dilation and curettage. No further information is available; the subject was lost to follow-up.

2.) **Subject 137-1012:** The subject was enrolled in study CP-OXYDET-08 and received her first dose of study drug (Oxycodone DETERx) in the titration phase of the study. On May 15, 2013, the subject was randomized to the Double-blind Maintenance Phase of the study and received placebo. The subject reported a positive home pregnancy test on July 31, 2013 and a reported last menstrual period of July 21, 2013. The subject was referred to her primary care physician for confirmation of her pregnancy but was lost to follow-up. There is no information about pregnancy outcome.
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/s/

MIRIAM C DINATALE
10/02/2015

TAMARA N JOHNSON
10/02/2015

LYNNE P YAO
10/05/2015

Reference ID: 3828060
****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2015

To: Ayanna Augustus, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208090
Xtampza ER (oxycodone extended-release) Capsules
Professional Labeling Review

As requested in DAAAP’s consult dated December 18, 2014, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for Xtampza ER Capsules. The substantially complete prescribing information was provided to OPDP on September 29, 2015, via email by Ayanna Augustus with the file name “draft-label-word-version_NDA 208090_14APR2015_Page Orientation_FINAL 9 29 15.docx”.

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made a comment on page 33.

OPDP has no comments on the carton and container labeling submitted September 24, 2015.

Please note that our comments on the Medication Guide will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).
Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KOUNG U LEE
10/05/2015
PATIENT LABELING REVIEW

Date: October 5, 2015

To: Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Koung Lee, RPh, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): XTAMPZA ER (oxycodone) extended-release capsules, for oral use, CII

Dosage Form and Route: Application Type/Number: NDA 208090
Applicant: Collegium Pharmaceutical, Inc.
1 INTRODUCTION
On December 12, 2014, Collegium Pharmaceutical, Inc. submitted for the Agency’s review a 505(b)(2) New Drug Application (NDA) 208090 for XTAMPZA ER (oxycodone) extended-release capsules, an abuse-deterrent, extended-release, microsphere-in-capule, oral formulation of the active ingredient oxycodone. The proposed indication for XTAMPZA (oxycodone) extended-release capsules is for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on January 14, 2015, for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) and Instructions for Use (IFU) for XTAMPZA ER (oxycodone) extended-release capsules.

2 MATERIAL REVIEWED
- Draft XTAMPZA ER (oxycodone) extended-release capsules MG received on December 12, 2014, and received by DMPP and OPDP on September 29, 2015.
- Draft XTAMPZA ER (oxycodone) extended-release capsules IFU received on December 12, 2014, and received by DMPP and OPDP on September 29, 2015.
- Draft XTAMPZA ER (oxycodone) extended-release capsules Prescribing Information (PI) received on December 12, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 29, 2015.

3 REVIEW METHODS
To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:
- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
• ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the MG meets the Regulations as specified in 21 CFR 208.20
• ensured that the MG and IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MORGAN A WALKER
10/05/2015

KOUNG U LEE
10/05/2015

BARBARA A FULLER
10/05/2015

LASHAWN M GRIFFITHS
10/05/2015
LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: September 10, 2015
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208090
Product Name and Strength: Xtampza ER (oxycodone) Extended-release Capsules 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Collegium Pharmaceuticals
Submission Date: December 12, 2014
OSE RCM #: 2014-2548
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD
DMEPA Associate Director: Irene Z. Chan, PharmD BCPS
1 REASON FOR REVIEW
As part of the approval process for Xtampza ER, DAAAP requested that we review the proposed container labels and package insert labeling for areas that may be vulnerable to confusion and can lead to medication errors. Xtampza ER (oxycodone) extended-release capsule is an opioid product with abuse deterrent properties, and Collegium Pharmaceuticals uses OxyContin as their referenced drug for their 505(b)(2) NDA application. In preparation for an upcoming Advisory Committee meeting, DAAAP also requested that we comment on the potential effectiveness of the labeling and packaging to mitigate the risks of taking Xtampza ER incorrectly on an empty stomach.

2 MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>N/A B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>N/A C</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>N/A D</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>N/A E</td>
</tr>
<tr>
<td>Other</td>
<td>N/A F</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Strength Equivalency and Salt Policy
Based on the Draft Guidance for Industry, Naming of Drug Products Containing Salt Drug Substances and discussions with Collegium and the FDA in the IND phase, the active ingredient must be expressed as the active moiety (oxycodone) rather than the equivalent salt (oxycodone hydrochloride).\(^1\)\(^2\) Thus, the equivalent strengths for Xtampza ER are different than the referenced product, OxyContin (see Table 2 below).

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\(^2\) Meeting Minutes, IND 075786, Submitted in DARRTS on May 16, 2014

Reference ID: 3817753
Table 2. Strength Conversion for Xtampza ER and OxyContin

<table>
<thead>
<tr>
<th>OxyContin (oxycodone hydrochloride) Strengths</th>
<th>Corresponding Xtampza ER (oxycodone) Strengths</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>9 mg</td>
</tr>
<tr>
<td>15 mg</td>
<td>13.5 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>18 mg</td>
</tr>
<tr>
<td>30 mg</td>
<td>27 mg</td>
</tr>
<tr>
<td>40 mg</td>
<td>36 mg</td>
</tr>
<tr>
<td>60 mg</td>
<td>No proposed strength. Equivalent dose would be 54 mg</td>
</tr>
<tr>
<td>80 mg</td>
<td>No proposed strength. Equivalent dose would be 72 mg</td>
</tr>
</tbody>
</table>

We are concerned that healthcare providers unfamiliar with the conversion between Xtampza ER (oxycodone) and OxyContin (oxycodone hydrochloride) may believe the dose for Xtampza ER is the same dose for OxyContin. This risk may be increased in settings where the product is ordered by its established name. For example, a prescriber upon hospital admission, instead of writing Xtampza ER, writes oxycodone ER 72 mg since the hospital uses the established name to order medications. However, a nurse or pharmacist would need to seek clarification because the strengths of other long acting oxycodone products are not available in these specific strengths and the doses cannot be readily achieved. During clarification, the prescriber would indicate that the patient is taking Xtampza ER and that this is an appropriate dose. The pharmacist and nurse would then make the appropriate strength and dose conversion with the prescriber. However, the strength conversion information in the Prescribing Information can be revised to improve readability of this important information to ensure that healthcare professionals can obtain the information in a format that is easier to read. We provide recommendations in Section 4.1 to improve the readability of the strength equivalency information in the Prescribing Information.

**Food Effect and Packaging Considerations**

Xtampza ER is dosed every 12 hours and must be administered with food to ensure plasma levels are consistent and similar to plasma levels seen with the administration of OxyContin (oxycodone hydrochloride). Co-administration with food increases the extent of absorption when compared to administration of the same drug in the fasted state. We provided comments on the potential effectiveness of packaging, approved labeling, and other written materials to mitigate the risk of administering Xtampza ER incorrectly on an empty stomach in a review submitted to the background package for an Advisory Committee Meeting held on September 11, 2015. Discussion can be found in OSE Review# 2015-864.³

³ Schlick J. Review Of Labels And Labeling For Collegium Pharmaceutical’s Oxycodone Extended-Release Capsules And The

Reference ID: 3817753
We are concerned that the inappropriate administration of Xtampza ER without food may result in an underdose and inadequate pain relief, or inconsistent types of food administered with the product may result in variability in serum levels and serious adverse events. Moreover, we are also concerned that the differences in absorption resulting from the food effect for Xtampza ER are clinically impactful, and we consider it very important to convey to the patient that the medication should be consistently taken with food. We considered packaging configurations of products that require administration with food to prevent wide variations in plasma concentrations, and found that some use a unit-of-use packaging configuration. This type of packaging configuration may provide a durable approach to help ensure patients see the proper administration instructions at the time that each dose is administered. In addition to having a positive statement “take with food” on the unit- of- use package, one such approach that can improve adherence is to utilize warning information on written materials, packaging and labeling that fully characterizes the severity of the hazard.

If unit of use packaging is considered during product development, the Sponsor would need to take into consideration packaging configurations that would be appropriate for the various patient regimens (i.e., acute treatment for 5 to 10 days versus longer term use of the product). They would have to overcome technical challenges that arise for the range of dosing and day supply for various patient regimens and when dispensing a controlled substance. However, there is no way to determine without further data that this recommendation or that the proposed labeling submitted for Xtampza ER is a mechanism that will ensure that patients will correctly administer the drug on a consistent basis. To ensure that the label, labeling, and packaging is optimized to provide a clear and consistent statement to the patient and is feasible for all patient regimens, a comprehensive risk analysis to examine the severity of the risk and the probability that it will occur and labeling comprehension study should be conducted to demonstrate that the administration instructions are well understood and risks associated with not following directions are clear to patients.

**Labeling Considerations**

For a full discussion on the impact of labeling with Xtampza ER administration, refer to OSE Review# 2015-864. However, as a brief summary, it is very important that critical information is consistently communicated to new patients prescribed opioid products or patients being switched between different ER/LA opioid products. A significant amount of this critical information is conveyed to the patient through written material like the Medication Guide. Given that ER/LA opioids historically can be taken without regard to food, we are concerned

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Associated Advisory Committee Meeting (NDA 208090) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 4. 8 p. OSE RCM No.: 2015-864.

Schlick J. Review Of Labels And Labeling For Collegium Pharmaceutical’s Oxycodone Extended-Release Capsules And The Associated Advisory Committee Meeting (NDA 208090) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 4. 8 p. OSE RCM No.: 2015-864.

Reference ID: 3817753
patients who have been on other ER/LA opioids may not read the written material for this proposed product because they feel they are already well-educated on ER/LA opioids. Thus, if the patient does not read the important information in the medication guide, there is risk for patients to take the medication without food.

We reviewed the Division of Risk Management’s (DRISK’s) patient survey data submitted as part of an assessment of the ER/LA REMS on February 26, 2015. According to DRISK’s review, for the medication guide, 90% of patients received them from the pharmacy. However, approximately 19% (16%+3%) of patients either did not read the medication guide, or only read some of it. The survey also included an assessment of patient comprehension of five key risk messages of ER/LA opioid analgesic products. DRISK concluded that there was generally a high understanding of key risk messages related to the product class. However, some information had a lower understanding of aspects of safe storage and using the drug safely. This suggests that not all important information is consistently recalled or read by patients receiving new prescriptions of ER/LA opioid analgesics.

Packaging and patient information labeling is often used to improve recall of and adherence to important prescribing information conveyed by healthcare professionals. However, from a failure mode perspective, packaging and patient information labeling is not a fail-safe measure because there is no way to ensure that the label is read, understood, or likely to be attended to. Thus, there is no way to determine without further data that the proposed labeling for the Collegium product is a mechanism that will ensure that patients will correctly administer the drug on a consistent basis.

Ultimately, DAAAP will make the determination if the benefits of this product outweigh the risks associated with the food effect. If DAAAP determines that the benefits outweigh the risks, then we provide recommendations to DAAAP on the use of unit of use packaging and the validation required to determine the safe and effective use of the label, labeling and proposed unit-of-use packaging.

**Other Considerations**

- The salt equivalency statement appears on the container label in accordance with the Guidance for Industry, Naming of Drug Products Containing Salt Drug Substances. Because of the food effect risk discussed in the previous section and the need to convey this critical information on the principal display panel with limited space, we recommend moving the salt equivalency statement to the side panel to make room for

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a critical warning statement about taking the product with food. We provide a recommendation in Section 4.2 to address this.

- The controlled substance symbol on the principal display panel distracts from other important information.

- The medication guide statement

- The modifier ‘ER’ on the principal display panel of the container label is a smaller font than ‘Xtampza’ which decreases the prominence of the dosage form characteristics of the product. We recommend in Section 4.2 to make the modifier font the same size as the capital letter ‘X’ in Xtampza to increase the prominence of the dosage form.

- Collegium proposes to introduce an extended release oxycodone tablet containing five strengths (9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg). We have not identified this to be a problem on the market, so we find the proposed strengths acceptable.

4 CONCLUSION & RECOMMENDATIONS

We are concerned that the currently proposed packaging, labels, and labeling do not appropriately mitigate the risk for administration errors due to the food effect. We recommend revised packaging, such as unit-of-use packaging, as a preferred intervention. If DAAAP determines unit-of-use packaging is an appropriate strategy, we recommend Collegium evaluate the feasibility of unit-of-use packaging, and submit a comprehensive risk analysis to examine the severity of the risk and the probability it will occur. Additionally, we recommend they conduct a label comprehension study to demonstrate that the administration instructions are well understood and risks associated with not following directions are clear to patients. We provide a recommendation for this in Section 4.1.

However, if DAAAP finds the current packaging, labels, and labeling acceptable to mitigate the risk associated with incorrectly administering Xtampza ER with respect to food, then we have recommendations for the current presentation in Section 4.1 and 4.2.
4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Recommendation on Unit-of-Use Packaging

1. If DAAAP determines that unit-of-use packaging is an appropriate strategy, we recommend that Collegium evaluate the feasibility of unit-of-use packaging, and submit a comprehensive risk analysis to examine the severity of the risk and the probability that it will occur. Additionally, we recommend they conduct a label comprehension study to demonstrate that the administration instructions are well understood and risks associated with not following directions are clear to patients.

B. Highlights of Prescribing Information, Dosage and Administration Section

1. Revise the first statement in this section to read as follows:

   Bold the font to increase the prominence of the statement

C. Full Prescribing Information, Dosage and Administration Section 2.1

1. Revise the first statement in this section to read as follows:

   Bold the font to increase the prominence of the statement.

2. Consider adding a table to include the equivalent dose of oxycodone and oxycodone hydrochloride. This would provide guidance for dose conversions between Xtampza ER and other oxycodone hydrochloride products. For example:
D. Full Prescribing Information, Dosage and Administration Section 2.5

1. Add numerals for each statement to indicate that these are steps on how to take with soft food/applesauce rather than bullet points.

2. Revise the first statement in this section to read as follows:

   Bold the font to increase the prominence of the statement.

E. Medication Guide, When taking XAMPZA ER Section

1. Revise the take with food statement and place the revised statement in bold font as follows:

F. Instructions for Use

1. Remove
4.2 RECOMMENDATIONS FOR COLLEGIUM PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

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 Xstampza 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:

   Always take with food. Taking on an empty stomach can decrease drug absorption
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.
Table 2 presents relevant product information for Xtampza ER that Collegium Pharmaceuticals submitted on December 12, 2014, and the listed drug (LD).

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Xtampza ER</th>
<th>OxyContin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval Date</td>
<td>N/A</td>
<td>April 5, 2010 under NDA 022272 which includes abuse deterrent properties</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>oxycodone</td>
<td>Oxycodone [hydrochloride]</td>
</tr>
<tr>
<td>Indication</td>
<td>Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</td>
<td>Same as Xtampza ER</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Oral</td>
<td>Same as Xtampza ER</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>Extended-release <strong>Capsule</strong></td>
<td>Extended-release <strong>Tablet</strong></td>
</tr>
<tr>
<td>Strength</td>
<td>9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg</td>
<td>10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg</td>
</tr>
<tr>
<td>Dose and Frequency</td>
<td>9 mg to 80 mg orally every 12 hours</td>
<td>10 mg to 80 mg orally every 12 hours</td>
</tr>
<tr>
<td>How Supplied/ Container Closure</td>
<td>Bottles of 100 with a child resistant closure</td>
<td>Bottles of 100 with a child resistant closure Unit dose card – 10 tablets per card</td>
</tr>
<tr>
<td>Storage</td>
<td>Room temperature</td>
<td>Same as Xtampza ER</td>
</tr>
</tbody>
</table>
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Xtampza ER labels and labeling submitted by Collegium Pharmaceuticals on December 14, 2014.

- Container Labels
- Instructions for Use - No image
- Medication Guide - No image

G.2 Label and Labeling Images

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


Reference ID: 3817753
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES H SCHLICK
09/10/2015

BRENDA V BORDERS-HEMPHILL
09/10/2015

LUBNA A MERCHANT on behalf of IRENE Z CHAN
09/10/2015
MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 9, 2015

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Oxycodone DETERx (Oxycodone ER Capsules), NDA 208-090
Xtampza ER Capsules1 – Capsules of oral administration containing oxycodone base at dosage strengths 9.0 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg.
(Oxycodone HCl equivalents are 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg)
IND Number: 75,786
Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.
Sponsor: Collegium Pharmaceutical Inc.
PDUFA Goal Date: October 12, 2015

Materials Reviewed:
Category 1, 2, and 3 studies, as well as other relevant information, necessary to assess the abuse-deterrent properties of Xtampza ER Capsules.

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   2. Conclusions.......................................................................................................................................2
   3. Recommendations.............................................................................................................................7

1 The Agency has approved the proprietary name as “Xtampza ER” (DARRTS, NDA 208-090, February 2, 2015, Author: V Jarral).
I. Summary

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to review from a CSS perspective NDA 208-090 submitted by Collegium Pharmaceutical Inc. for Xtampza Extended Release (ER) Capsules (Oxycodone ER Capsules) previously known as Oxycodone DETERx. This product is formulated as capsules for oral administration containing oxycodone base at dosage strengths of 9.0 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg. The drug product is indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

Xtampza ER Capsules was developed under IND 75,786. This product has not previously been marketed in the United States or other countries. Due to the presence of oxycodone, Xtampza ER Capsules is in Schedule II of the Federal Controlled Substances Act.

2. Conclusions

1. Overall Findings: Results of Category 1, 2, and 3 studies suggest that Xtampza ER Capsules are difficult to manipulate and may provide resistance to abuse by intranasal administration. Xtampza ER Capsules microspheres are difficult to crush (Category 1). Results of Category 2 study CP-OXYDET-19 demonstrated intranasal Xtampza ER 40 mg crushed produced maximum oxycodone plasma level lower than that produced by oral intact Xtampza ER 40 mg or by 40 mg oxycodone powder intranasal. In Category 3 study CP-OXYDET-21, intranasal crushed Xtampza ER 40 mg, when compared to intranasal oxycodone 40 mg powder, produced a lower peak plasma concentration of oxycodone (C_{max}) as well as significantly lower levels of drug liking and high as determined using the Drug Liking VAS and High VAS, respectively.

2. Overall Findings: Based on the studies conducted it is not clear whether Xtampza ER 40 mg Capsules provides a clinically meaningful deterrent effect to oral abuse. Results of Category 1 and 2 studies suggest possible resistance of Xtampza ER Capsules to oral abuse following crushing or
chewing. Xtampza ER microspheres are difficult to crush and resist dumping of oxycodone into aqueous solution under varying conditions of temperature or agitation. Category 2 studies CP-OXYDET-17 and CP-OXYDET-25 demonstrate that oral crushed or chewed Xtampza ER is associated with significantly lower oxycodone $C_{\text{max}}$ than that from the positive comparator IR oxycodone HCl solution. However, in Category 3 study CP-OXYDET-24, the results obtained regarding subjective effects including drug liking were such as to question any clinical significance of the differences observed between chewed Xtampza ER and the IR oxycodonc HCl crushed oral solution. This was the case even though these differences were statistically significantly different.

3. Xtampza ER 40 mg microspheres effectively resist particle size reduction using a variety of tools. Most effective tool to crush Xtampza ER microspheres is the mortar and pestle. By contrast, Roxicodone was crushed using all tools examined indicating no resistance to crushing. Some particle size reduction of OxyContin OP tablets was achieved using several tools, with the cheese grater being the most effective tool.

4. Xtampza ER 40 mg microspheres, intact or crushed, resisted dumping of oxycodone in 30 mL of water held at room temperature or elevated temperature (37°C or 60°C) as evidence by <16% label claim (LC) extraction of oxycodone. OxyContin OP 40 mg tablets were more susceptible to oxycodone extraction as evidenced by the recovery of between 57.4% LC and 80.7% LC oxycodone following just 15 minutes extraction of crushed OxyContin in water held at room temperature, 37°C, or 60°C. Extraction of oxycodone was rapid from Roxicodone 30 mg tablets (whole or crushed), as would be expected from an immediate release formulation.

5. Intact Xtampza ER 40 mg microspheres and intact OxyContin OP 40 mg maintained controlled release properties in 30 mL “ingestable” solvents such as Coca-Cola, 40% ethanol, vinegar, and pH 4.9 water held at room temperature. At 2 hours of extraction in these solvents, oxycodone recovery from Xtampza ER microspheres ranged from 1.0% LC to 1.9% LC (exception of 26.8% LC recovered in 40% ethanol) while from intact OxyContin OP tablet recovery was in range of 23% LC to 29% LC.

6. Under conditions of agitation, using Coke, Vinegar, 40% ethanol, or pH 4.9 water %LC oxycodone recovered from crushed Xtampza microspheres was less than 19% at 1 hour of extraction. In contrast, with use of crushed OxyContin OP tablets exposed to the same solvents, %LC of oxycodone recovered was in the range of 75.7% to 82.3% with just 0.25 hours of extraction. Xtampza ER microspheres, compared to OxyContin OP tablets, demonstrated a greater resistance to the effects of crushing on dose dumping of oxycodone.

7. With the combination of crushing and elevated solvent (ingestible) temperature, some compromise of the controlled release properties for oxycodone of Xtampza ER microspheres was observed. The most efficient means to extract oxycodone from crushed Xtampza ER microspheres was use of either coke or vinegar held at 60°C. With 1 hour of extraction, greater that 80% LC of oxycodone was extracted. With use of the same solvents under identical conditions, greater than 90% LC of oxycodone was extracted from OxyContin OP tablets.

8. Organic solvents were effective in the rapid extraction of oxycodone from Xtampza ER 40 mg microspheres. With use of the organic solvents, acetone, ethyl acetate, or methanol, oxycodone
recovery from intact or crushed Xtampza microspheres was greater than 69% LC with just 15 minutes of extraction. Methanol proved the most effective solvent with total oxycodone recovery (100% LC) from crushed Xtampza microspheres in 15 minutes of extraction. In contrast, with intact OxyContin OP tablets, using the same organic solvents there was less than 5% LC oxycodone extracted at 15 minutes. In the case of crushed OxyContin OP tablets, extraction for 15 minutes with acetone, ethyl acetate, and methanol resulted in oxycodone recovery of 54.2% LC, 6.4% LC, and 96.6% LC, respectively.

9. Under the various conditions utilized in the Category 1 intravenous studies, Xtampza ER 40 mg tablets, whether intact or crushed, could not be used to produce a solution suitable for intravenous injection due to the low recovery (<12% LC) of oxycodone in 2 mL, 5 mL, or 10 mL deionized water with immediate or delayed (out to 30 minutes) extraction. At the same time a high percentage of the water was recovered resulting in solutions with very low concentrations of oxycodone, not likely suitable for producing subjective reinforcing effects (drug liking) upon injection. With use of 40 mg OxyContin OP tablets, intact or crushed, there tended to be a greater recovery of oxycodone (maximum of 44% LC) compared to recovery from Xtampza ER 40 mg microspheres (intact or crushed); however, the resulting solutions were generally too dilute with respect to oxycodone concentration to be suitable intravenous solutions. Additional steps would be required to concentrate these solutions which might, however, result in an increased viscosity. Due to the rapid recovery of oxycodone from intact or ground Roxicodone, it was possible with use of just 2 mL of deionized water to produce a solution suitable for intravenous injection. (See Table 2 for Immediate Preparation)

10. In a simulated smoking study, exposure of crushed samples to 250°C for 10 minutes resulted in oxycodone recovery in condensed vapor in the following ranges: 58.6% LC to 59.2% LC from Xtampza ER 40 mg microspheres; 34.5% LC to 37.8% LC from Roxicodone 30 mg; and 31.7% LC to 33.8% LC from OxyContin OP 40 mg. With the higher levels of oxycodone recovery in vapor observed with heating Xtampza ER microspheres, it is possible this product may be susceptible to abuse by smoking.

11. In Category 2 study CP-OXYDET-19, intranasal crushed Xtampza ER 40 mg produced an oxycodone C\text{max} (38.1 ng.mL) that was significantly lower than the oxycodone C\text{max} produced by either oral intact Xtampza ER (47.5 ng/mL) or 40 mg oxycodone powder (63.9 ng/mL). Total oxycodone exposure as expressed by AUC_{inf} was similar for the three treatments. (See Table 4 under Discussion)

12. In Category 2 study CP-OXYDET-25, with oral administration under fed conditions, crushed Xtampza ER 40 mg resulted in a plasma oxycodone C\text{max} (62.9 ng/mL) that was similar to the C\text{max} produced by intact Xtampza ER 40 mg (67.5 ng/mL) but statistically significantly lower than the oxycodone C\text{max} produced by crushed IR oxycodone 40 mg (79.4 ng/mL). This suggests a resistance to dose dumping following crushing of Xtampza ER microspheres. In contrast, crushing of 40 mg OxyContin OP resulted in substantial oxycodone dose dumping following oral administration as evidenced by C\text{max} of 78.4 ng/mL compared to an oxycodone C\text{max} of 64.9 ng/mL following oral administration of intact OxyContin OP 40 mg tablet. (See Table 5 under Discussion)
13. In Category 2 study CP-OXYDET-17, under fed conditions, oral administration of intact, crushed, or chewed Xtampza ER 40 mg produced similar oxycodone $C_{\text{max}}$ (range 55.6 to 62.3 ng/mL), all three of which were significantly less than the oxycodone $C_{\text{max}}$ resulting from oral 40 mg oxycodone HCl IR solution. Bioavailability of oxycodone was reduced when Xtampza ER 40 mg (intact, crushed or chewed) was administered under fasted conditions as evidenced by the lower oxycodone $C_{\text{max}}$ values in the range of 30.7 ng/mL to 41.1 ng/mL. This was also evidence in terms of the lower total oxycodone exposure under fasted conditions (range 369 hr*ng/mL – 422 hr*ng/mL) compared to fed conditions (range of 553 hr*ng/mL – 561 hr*ng/mL) as expressed by the AUC$_{\text{inf}}$. These overall pharmacokinetic data indicate a resistance of Xtampza ER formulation to oxycodone dose dumping following mechanical manipulation by crushing (mortar and pestle) or by chewing. (See Table 3 under Discussion)

14. In Category 3 study CP-OXYDET-24, Xtampza ER 40 mg administered intact or chewed under fasted or fed conditions produced mean peak plasma oxycodone levels ($C_{\text{max}}$) (range of 30.9 ng/mL to 41.9 ng/mL) that were significantly lower and appeared significantly later ($T_{\text{max}}$) (median range of 3.07 hours to 5.12 hours) than that produced by IR Oxycodone 40 mg solution fasted ($C_{\text{max}}$ of 77.7 ng/mL, median $T_{\text{max}}$ of 1.08 hours), thereby indicating a lack of bioequivalence. The AUC$_{0-3\text{hrs}}$ associated with IR Oxycodone 40 mg solution fasted (111.58 h·ng/mL) was also significantly higher than that produced by the Xtampza ER 40 mg treatments (range of 5.29 h·ng/mL to 33.98 h·ng/mL). (See Table 7)

15. In study CP-OXYDET-24, using the primary measure of bipolar Drug Liking VAS, chewed Xtampza ER 40 mg, whether administered under fed or fasted conditions, produced maximum drug liking (LS mean $E_{\text{max}}$ of 70.73 mm and 73.83 mm, respectively) that was statistically significantly ($p<0.0007$) less than the maximum drug liking produced by crushed IR Oxycodone HCl 40 mg solution fasted (LS mean $E_{\text{max}}$ of 81.56 mm) but statistically significantly ($p<0.05$) greater than that reported following placebo treatment (LS mean of $E_{\text{max}}$ of 54.70 mm). The $E_{\text{max}}$ of Drug Liking (81.56) produced by crushed IR Oxycodone 40 mg solution fasted seem to be low. With the limited differences (10.83 mm and 7.73 mm) in LS mean of $E_{\text{max}}$ for Drug Liking observed between fasted or fed chewed Xtampza ER 40 mg versus crushed IR Oxycodone 40 mg solution, it is not clear what is the clinical significance of the study results, regardless of the fact that these differences were statistically significant. (See Table 9)

16. In study CP-OXYDET-24, using the secondary measure of unipolar High VAS, chewed Xtampza ER 40 mg, administered under fed or fasted conditions, produced maximum high (LS mean $E_{\text{max}}$ of 37.70 mm and 45.56 mm, respectively) that was significantly ($p<0.0001$) below the maximum high produced by crushed IR Oxycodone 40 mg solution fasted (LS mean $E_{\text{max}}$ of 68.32 mm) but significantly ($p<0.05$) above that reported following placebo treatment (LS mean of 9.87 mm). These results, using a secondary measure, suggest a possible deterrent effect of Xtampza ER Capsules to abuse by chewing. (See Table 12 under Discussion)

17. In study CP-OXYDET-24, the results obtained using the Take Drug Again VAS did not support an oral abuse deterrent claim for Xtampza ER Capsules with respect to chewing. For all active treatments, LS mean $E_{\text{max}}$ values for Take Drug Again ranged from 68.85 mm to 74.73 mm. These scores were significantly greater than that produced by placebo (LS mean of 51.79 mm) indicating some willingness by the subjects to take each of the active treatments again, if given the opportunity.
Compared to treatment with crushed IR oxycodone HCl 40 mg solution fasted, there was a statistically significant reduction in take drug again following chewed Xtampza ER 40 mg under fed conditions; however this difference was small, raising the question of clinical significance. No statistical difference was observed in LS mean $E_{\text{max}}$ between chewed Xtampza ER 40 mg was given under fasted conditions versus treatment with crushed IR oxycodone 40 mg solution fasted. Data from the Take Drug Again VAS do not support a possible deterrent effect of Xtampza ER Capsules to abuse by chewing. (See Table 14 under Discussion)

18. In study CP-OXYDET-24, using the secondary measure of ARCI/MBG subscale, the overall results were not sufficient to provide support for an oral abuse deterrent claim for Xtampza ER. The positive control, crushed IR Oxycodeone 40 mg oral solution, produced a maximum LS mean score on this scale of only 7.25 out of a possible 16 total points. Chewed Xtampza ER 40 mg produced maximum scores under fed (LS mean = 4.35) and fasted (5.22) conductions that were statistically significantly lower than that produced by crushed IR Oxycodeone 40 mg in solution (LS mean = 7.25). However the differences in the scores between chewed Xtampza ER 40 mg, whether under fed (difference of 2.89) or fasted (difference of 2.03) conditions, and crushed IR Oxycodeone 40 mg in solution are small thereby raising the question of any clinical significance associated with these differences. (See Table 16 under Discussion)

19. Pharmacokinetic analysis in study CP-OXYDET-21 demonstrated that intranasal administration of IR Oxycodeone HCl produced a maximum oxycodone plasma concentration ($C_{\text{max}} = 60.9$ ng/mL) that was significantly greater than that produced following either Xtampza ER intranasal or intact oral Xtampza ER. $C_{\text{max}}$ following IR Oxycodeone HCl was achieved sooner (median $T_{\text{max}}$ of 2.58 hours) than the $C_{\text{max}}$ following treatment with Xtampza ER administered intranasally or orally (median $T_{\text{max}}$ of 5.08 hours). Total oxycodone exposure over the first 3 hours post-dosing, expressed in terms of $AUC_{0-3hrs}$ was significantly higher following IR Oxycodeone HCl IN (141 hr·ng/mL) compared to Xtampza ER either intranasal or orally administered (41.4 and 25.0 hr·ng/mL, respectively). (See Table 18 under Discussion)

20. In study CP-OXYDET-21, intranasal administration of crushed 40 mg Xtampza ER produced an $E_{\text{max}}$ of Drug Liking (LS mean of 61.88 mm) that was statistically significantly lower than that produced by 40 mg IR Oxycodeone (LS mean of 82.57 mm) (p<0.0001) or by oral 40 mg Xtampza ER (LS mean of 67.87 mm) (p=0.343). The $E_{\text{max}}$ of drug liking provided by intranasal Xtampza ER 40 mg was statistically (p<0.05) significantly higher than that produced by placebo (LS mean of 54.63); however, the difference in LS mean of $E_{\text{max}}$ (7.25 mm), is small thereby raising the question of clinical significance. With intranasal Xtampza 40 mg the time to reach $E_{\text{max}}$ was significantly (longer) compared to the time to reach $E_{\text{max}}$ following intranasal 40 mg IR oxycodone. These results suggest a potential deterrent effect of Xtampza ER Capsules to intranasal abuse. (See Table 20 under Discussion)

21. In study CP-OXYDET-21, using the secondary measure of High VAS, intranasal Xtampza 40 mg produced a high (LS mean of 23.78 mm) that was statistically significantly (p<0.0001) lower than the high produced by intranasal 40 mg IR oxycodone (LS mean of 69.05) but statistically similar (p>0.05) to that produced by placebo (LS mean of 14.59 mm). These results further support a possible deterrent effect of Xtampza ER Capsules to intranasal abuse. (See Table 22 under Discussion)
22. In study CP-OXYDET-21, using the secondary measure of bipolar Take Drug Again VAS, intranasal Xtampza ER 40 mg produced a LS mean score of 47.78 mm that was statistically significantly (p<0.0001) lower than the score produced by intranasal 40 mg IR oxycodone HCl (LS mean of 71.24) but statistically similar (p>0.05) to that produced by placebo (LS mean of 46.24). So whereas subjects expressed some willingness to take again intranasal 40 mg IR oxycodone HCl, they did not have an interest in taking again if given the opportunity intranasal crushed Xtampza ER Capsules. These results further support a possible deterrent effect of Xtampza ER Capsules to intranasal abuse. (See Table 23 under Discussion)

23. In study CP-OXYDET-21, using the secondary measure of the ARCI/MBG scale, intranasal Xtampza ER 40 mg produced a LS mean score of 1.57 that was statistically significantly (p=0.0001) lower than the score (5.92) resulting from treatment with intranasal IR oxycodone HCl 40 mg but was similar (p>0.05) to the score produced by placebo. The results using the ARCI/MBG scale are consistent with the other measures (Drug Liking VAS, Take Drug Again VAS, and High VAS), suggesting a possible deterrent effect of Xtampza ER Capsules to intranasal abuse. However, the positive control (IR oxycodone HCl 40 mg) produced a relatively low score of only 5.92 out of a possible total of 16. It is not clear whether the results obtained using the ARCI/MBG scale reflect a clinically relevant response. (See Table 24 under Discussion)

3. Recommendations

At this time CSS does not have any recommendations concerning Xtampza ER Capsules submitted under NDA 208-090.

II. Discussion

1. Chemistry

1.1 Substance information

Xtampza ER Capsules, is under development as a abuse-deterrent, oxycodone extended-release (ER) capsule oral formulation. Xtampza ER capsules are manufactured in five strengths including capsule including 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg oxycodone base. The oxycodone HCl equivalent for each of these strengths is 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg.

The Xtampza ER capsule formulation contains microspheres with a median particle size of approximately [60|6] microns. The microspheres contain oxycodone [40|4]
The quantitative composition of the five dosage strengths for Xtampza ER capsules is provided in Table 1.

Table 1. Quantitative Composition of Xtampza ER Capsules (Source: Table 1 on pages 5 and 6 of Description and Composition of the Drug Product, Module 3.2.P.1)

<table>
<thead>
<tr>
<th>Components</th>
<th>Dosage Strength (Oxycodone HCl Equivalent)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg</td>
<td>15 mg</td>
<td>20 mg</td>
<td>30 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Oxycodone Base</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myristic Acid</td>
<td></td>
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<tr>
<td>Yellow Beeswax</td>
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<tr>
<td>Carnauba Wax</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stearoyl Polyoxy-32 Glycerides</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Colloidal Silicon Dioxide</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hyromellose Capsule Shell</td>
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<td></td>
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</tr>
</tbody>
</table>

Microsphere excipients and their concentrations were intended to:

...
1.3 In vitro manipulation and extraction studies for products with Abuse-Deterrent features

Sponsor conducted a series of in vitro physical manipulation and chemical extraction studies as part of the pre-market assessment of possible abuse-deterrent effects of Xtampza ER capsules. These studies were conducted on 40 mg Xtampza Capsules with comparison to 30 mg Roxicodone tablets and 40 mg OxyContin OP tablets.

The CDER Office of Pharmaceutical Quality (OPQ) reviewed all in vitro studies conducted by Sponsor on Xtampza ER capsules and provide a report of their review to CSS. Information contained within the OPQ report, as well as information from the various in vitro study reports submitted by the Sponsor under NDA 208-090 were used to evaluate the in vitro studies for this review. A copy of the OPQ review of the in vitro studies is appended to this review.

The Sponsor conducted a number of different in vitro studies to assess the use of Xtampza ER microspheres in preparing aqueous solutions suitable for intravenous injection. For purposes of this review, these studies will be evaluated in terms of the results obtained by Stoops et al., (2010)2. Using a double-blind, within-subject, randomized, placebo-controlled study design, Stoops et al., (2010) examined the subjective effects of intravenous injection of oxycodone HCl (5 mg, 10 mg, and 20 mg) on subjective effects, including Drug Liking (visual analog scale), in non-dependent, recreational opioid users with a history of intravenous opioid use. Intravenous injection of 10 mg or 20 mg oxycodone HCl, but not 5 mg oxycodone HCl produced levels of drug liking that were significantly above that produced by placebo. These data suggest that a solution suitable for intravenous injection should contain at around 10 mg of oxycodone HCl, which is likely to produce sufficient reinforcing effects such as drug liking.

Study 1. Physical Manipulation

Sponsor examined the use of the following tools to reduce the particle size by crushing, grinding, or grating of Xtampza ER microspheres, Roxicodone tablets and OxyContin OP tablets: rotating food chopper, blade based pill cutter, cheese grater, mortar and pestle, hammer, metal garlic press, pill crusher (with teeth), pepper mill, herb mill, and coffee grinder. Particle sized distribution was determined using a Malvern Masterizer S Laser Diffraction Particle Size Analyzer with Dry Powder

Feeder. Dissolution studies on manipulated samples were conducted using a Distek USP Dissolution Apparatus II (Paddle).

**Physical Manipulation of Xtampza ER Microspheres**

Xtampza ER capsules contain waxy beads (microspheres) that are approximately \( \mu m \) in diameter. In the absence of manipulation (controls), the particle size distribution is \( D_{10} \) \( \mu m \), \( D_{50} \) \( \mu m \), and \( D_{90} \) \( \mu m \).

The challenge in selecting tools to effectively reduce the particle size (manipulate) of the Xtampza ER microspheres are finding tools to physically engage the microspheres. The fine grater, tablet crusher, herb mill, pill splitter and garlic presses could not engage the microspheres, thereby making them of no use in manipulating Xtampza ER. Use of Coffee grinder, pepper mill, tablet crusher, and food chopper resulted in less than a 10% change in particle size distribution of the microspheres. In dissolution studies, microspheres manipulated with these tools did not show dose dumping (fast and significant release) of oxycodone. The hammer produced some particle size reduction.

Of the tools examined, grinding with the mortar and pestle was the most effective means for reducing the particle size of the microspheres. Additional studies using various grinding times demonstrated that the maximum particle size reduction was achieved with 2 minutes of grinding using the mortar and pestle. The resulting particle size distribution was \( D_{10} 139 \mu m \), \( D_{50} 263 \mu m \), and \( D_{90} 415 \mu m \). In dissolution studies, microspheres ground with mortar and pestle demonstrated an approximately 20% enhancement of oxycodone release compared to non-manipulated microspheres, indicating minimal dose dumping.

**Physical Manipulation of OxyContin OP Tablets**

Eight of the 11 tools applied to OxyContin OP impacted the integrity of the tablet which at a minimum produced deformations, while in the worst case reducing the tablet into small chunks or particles. The fine grater proved to be the most effective tool in reducing the particle size of the OxyContin OP tablet. Reducing the OxyContin OP tablets to small chunks or lower particle sizes resulted in noticeable increases in release of oxycodone (dose dumping). So, for example, at 1 hour of dissolution, the average percent release of oxycodone was approximately 18% from intact (non-manipulated tablet) but approximately 80% from tablets manipulated with a fine grater.

**Study 2. Part A. Syringeability - Preparation for Intravenous Administration – Use of Ground 40 mg Xtampza ER Microspheres, Ground Roxicodone 30 mg and Ground 40 mg OxyContin OP Tablets.**

In this study crushed drug product was transferred to a scintillation vial with 5 mL or 10 mL water (room temperature) and shaken for 5 seconds. The solution was drawn into a 5 cc or 10 cc syringe fitted with one of four different sized needles: 18 gauge (g), 22 g, 25 g, or 27 g. The solution was expelled through the attached needle, the volume measured, and the sample diluted and analyzed to determine the drug content in the syringed volume. The present study was thus aimed at quantifying the volume of liquid that was expelled through the syringe, as well as the quantity of drug in the expelled volume.
Application of a single ground (mortar and pestle, 2 minutes, 100 rpms) Xtampza tablet to 5 mL or 10 mL of water in a scintillation vial resulted in two layers, namely a lower water layer and an upper layer containing crushed Xtampza (waxy layer). With initial application of 5 mL water, approximately 4.5 mL was aspirated using 18g or 22 g needles and 1.5 mL aspirated using 25 g and 27 g needles. Following addition of 10 mL water, use of a 25 g or 27g needle resulted in recovery of about 1 mL, while use of a 22 g or 18 g needle provided recovery of 4 and about 9.2 mL, respectively. Analysis of the aspirated volume showed not more than 1.4% LC of oxycodone extracted and therefore not being suitable for intravenous injection.

Addition of ground (grated) OxyContin OP tablet to water resulted in a solution of increased viscosity from which only a limited volume could be aspirated. Using 5 mL of water and the three largest diameter needles tested (25 g, 22 g, and 18 g), the liquid aspirated ranged from 2.4 mL to 4.0 mL and consisted of oxycodone recovery in the range of 26.1% LC to 44.2% LC. These solutions would be too dilute to be effectively abused by intravenous injection, assuming 1 mL or less of solution was injected.

Crushed Roxicodone in 5 mL or 10 mL of water at room temperature provided no barrier to syringeability using any gauge needle, resulting almost complete recovery of water (5 mL or 10 mL). With use of all gauge needles the average range of recovery of oxycodone was 80% LC to 89% LC. These solutions may be too dilute to produce subjective effects when 1 mL or less of solution is intravenously injected.

Study 2. Part B. Syringeability – Preparation for Intravenous Administration – Use of Intact 40 mg Xtampza Microspheres and Molten Microspheres

Intact microspheres were transferred from a Xtampza ER capsule into a syringe barrel, followed by addition of 5 mL of water. Following mixing attempts were made to expel the resulting suspension through 18, 22, and 27 gauge needles. Expelled beads were collected and weighed. In this study it was only with the 18 gauge needle that intact microspheres could be ejected from the syringe.

It was not possible to eject from a syringe molten microspheres produced by heating.

These observations indicate that intact and molten microspheres cannot be intravenously injected for purposes of abuse.

Study 3. Small Volume Extraction – Preparation for IV Injection – Immediate Sample Preparation and Analysis – Ground 40 mg Xtampza ER Microspheres, Ground 40 mg OxyContin OP Tablets, and Ground 30 mg Roxicodone Tablets

Sponsor examined the ability to produce from single ground products a suitable intravenous solution using 2, 5, and 10 mL of water held at either room temperature or at the boiling point. With the exception of the time to bring to boil, there was no extraction duration used in the preparation of the solutions.
For studies using room temperature water, ground products were placed into a 10 cc syringe with a
cotton plug in its tip as a filter (Xtampza ER and OxyContin OP) or in a scintillation vial (Roxicodone).
The appropriate volume (2 mL, 5 mL, or 10 mL) of deionized water was added. Sample was filtered
into a new scintillation vial. Volume and weight of collected samples were determined following
analysis for oxycodone.

For studies using boiling water, crushed product was placed into a scintillation vial with 2 mL, 5 mL, or
10 mL deionized water. Vial was placed on a hot plate set at 350°C until water began to boil.
Roxicodone and Xtampza ER samples were allowed to cool prior to filtering. OxyContin OP filtration
was carried out while sample was hot. Samples were filtered into a clean scintillation vial. Volume and
weight of collected samples was determined followed by analysis for oxycodone.

Results are shown in Table 2. Under all three solvent volume conditions, there was a substantial
recovery of liquid using the 27 gauge needle for aspiration. This was particularly the case using crushed
Xtampza ER microspheres and Roxicodone, suggesting little if any issue with viscosity. The limited
percentage recovery of liquid (range of 50% to 74%) in the case of OxyContin OP in water at boiling
suggested possible increased viscosity due to gelling.

Across all three solvent volumes held at either room temperature or boiling, the percentage recovery of
oxycodone from crushed Xtampza ER was very low, ranging from 0.1% LC to 4.2% LC. With this low
oxycodone recovery, the resulting solutions would not be suitable for intravenous injection.

Across all three solvent volumes held at either room temperature or boiling, the percentage recovery of
oxycodone from ground OxyContin was in the range of 4.2% LC to 20.9% LC, which was somewhat
higher than that using crushed Xtampza ER. However, the resulting solutions, containing limited
oxycodone (maximum 8.3 mg in 9.3 mL) in multiple milliliters of solution would most likely not be
suitable solution for intravenous injection (not producing subjective effects such as drug liking).

Table 2. Average Percentage Label Claim Oxycodone Recovered and Milliliters (mL) of Liquid
Aspirated Using a 27g Needle Following Exposure of Crushed Products to 2 mL, 5 mL, and 10 mL
Water. (In this study, the preparation of solution was immediate with no extended extraction durations.)

<table>
<thead>
<tr>
<th>Crushed Products</th>
<th>2 mL Water</th>
<th>5 mL Water</th>
<th>10 mL Water</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average % Oxycodone Recovered</td>
<td>Average mL Collected 27 g Needle</td>
<td>Average % Oxycodone Recovered</td>
</tr>
<tr>
<td>Water Held At Room Temperature – NO Extraction Duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xtampza 40 mg</td>
<td>0.1</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>OxyContin 40 mg</td>
<td>4.2</td>
<td>1.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Roxicodone 30 mg</td>
<td>62.0</td>
<td>1.7</td>
<td>73.9</td>
</tr>
<tr>
<td>Water at Boiling Point – No Extraction Duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xtampza 40 mg</td>
<td>1.2</td>
<td>1.6</td>
<td>2.6</td>
</tr>
<tr>
<td>OxyContin 40 mg</td>
<td>8.5</td>
<td>1.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Roxicodone 30 mg</td>
<td>78.8</td>
<td>1.6</td>
<td>89.1</td>
</tr>
</tbody>
</table>
Across all three solvent volumes held at either room temperature or boiling, the percentage recovery of oxycodone from crushed Roxicodone was fairly high ranging from 62% LC to 94.8% LC. The resulting solutions using 2 mL of water, with oxycodone concentrations of 10.9 mg/mL (room temperature conditions) and 14.78 mg/mL (boiling temperature) should be suitable for intravenous abuse, assuming the volumes (1.6 and 1.7 mL) were injected. With use of 5 mL and 10 mL water volumes, the resulting solutions would be too low an oxycodone concentration to be suitable for intravenous injection unless either multiple milliliters were injected or time was allowed for removing water (evaporation) from the solutions.

Attempts to Use 10 mg and 20 mg Xtampza ER Crushed Microspheres to Produce Intravenous Solution

Sponsor repeated the study conditions using also 10 mg Xtampza ER microspheres and 20 mg Xtampza ER microspheres. With use of either product strength the recoverable oxycodone was less than that obtained using 40 mg Xtampza ER microspheres. Under the experimental conditions used, the 10 mg and 20 mg Xtampza ER capsules could not be used to produce a suitable solution for intravenous abuse.

Pre-Heated Samples of Ground Xtampza ER Microspheres and Ground OxyContin

One additional sub-study conducted was to attempt preparation of a suitable intravenous solution using Xtampza 10 mg, 20 mg, and 40 mg crushed microspheres and from crushed 40 mg Oxycodone that were thermally pretreated. Each product powder was heated to 180°C using a hotplate. After cooling, samples were placed in a scintillation vial with 5 mL of water. The water was then brought to boil on a hotplate followed by cooling and filtering in the case of Xtampza ER samples. OxyContin samples were filtered while hot. Volume aspirated using a 27 gauge needle was determined. Aspirated liquid was subjected to quantitative analysis of oxycodone.

The percentage recovery of oxycodone from the pre-heated ground samples of Xtampza ER microspheres (10 mg, 20 mg or 40 mg), was too low (range 1.7% LC to 5.1% LC) to produce suitable solutions for intravenous injection.

With respect to use of preheated, finely crushed 40 mg OxyContin, 27.12 mg (67.8% LC) oxycodone was recovered in 4.7 mL of aspirated liquid resulting in an oxycodone concentration of 5.77 mg/mL. To be effective for intravenous abuse, either multiple mL of the solution would have to be injected or steps would be required to reduce the solution volume.

Study 4. Small Volume Extraction – Preparation for IV Injection - Delayed Sample Preparation and Analysis – Intact and Crushed 40 mg Xtampza ER Microspheres, 40 mg OxyContin, and 30 mg Roxicodone.

In this study attempts were made to produce suitable intravenous solutions using intact and crushed product samples following extraction in 5 mL or 10 mL water for durations of 0.5, 2, 5, 15, and 30 minutes, or until >80% LC was recovered. Extractions were done in scintillation vials with water held either at room temperature or at 90°C-95°C. For some extractions, Xtampza ER and OxyContin OP ground samples were pre-heated (8 minutes in microwave under full power). Products were allowed to
cool prior to attempts at extraction. Viscosity of each sample was determined using a Brookfield viscometer.

Extraction With Water at Room Temperature

With use of 5 mL or 10 mL water at room temperature and extraction out to 30 minutes, the recovery of oxycodone from intact or crushed Xtampza ER microspheres was too low to result in a solution suitable for intravenous abuse. Maximum oxycodone recovered from intact and crushed Xtampza in 5 mL water was only 2% LC. With an increase to 10 mL water, maximum oxycodone recovery was 2.8% LC. In each case, the recoverable liquid was high (>80%) with a viscosity similar to water.

The release of oxycodone from intact OxyContin OP was slow with oxycodone recovery at 30 minutes of extraction of only 9.9% LC from 5 mL in water and 9.3% LC in 10 mL of water. The amount of liquid recovered was >90%, with a viscosity similar to water. With low recovery of oxycodone and large solution volume, these solutions would not be suitable for intravenous abuse.

With use of crushed OxyContin, maximum average recovery of oxycodone was 28.5% LC (11.4 mg) and 38.7% LC (15.5 mg) using 5 mL and 10 mL of water at room temperature, respectively. From an initial volume of 5 mL and 10 mL water, the recovered liquid was 2.3 and 7.4 mL, respectively. There was some increase in viscosity of these solutions. With the low oxycodone concentrations of these solutions, to be effective for intravenous abuse, would require either the injection of multiple milliliters of solution, or initial reduction in solution volume be evaporation of some of the water.

As expected with an immediate release formulation with no abuse deterrent features, >93% LC of oxycodone was recovered within 15 minutes from intact tablets and >86% LC of oxycodone was recovered with 0.5 minutes from crushed tablets using 5 mL or 10 mL of room temperature water. There was >90% recovery of liquid having a viscosity similar to water. Due to the limited concentrations of oxycodone in these solutions, to be suitable for intravenous abuse, either multiple milliliters would have to be injected or the solutions would have to be concentrated by loss of water.

Extraction with Water at 90°C-95°C

Extraction of intact and Xtampza microspheres with 5 mL and 10 mL water at elevated temperature, maximums of only 6.2% LC and 10.8% LC of oxycodone was recovered, respectively. With use of crushed Xtampza microspheres oxycodone recovery was 5.9% LC (2.4 mg) and 11.2% LC (4.5 mg) using 5 mL and 10 mL water, respectively. At the same time greater than 95% of the water was recovered with a viscosity similar to water. Do to the very low recovery of oxycodone these solutions would not be suitable for intravenous abuse.

The recovery of oxycodone from crushed OxyContin reached a maximum of 36.6% LC (14.6 mg) at 2 minutes of extraction in 5 mL water at 90°C-95°C, with recovery of 2.2 mL (44% of 5 mL) of liquid. Assuming individuals were willing to inject the 2 mL of solution, this solution might well result in subjective drug liking effects. With longer extraction times oxycodone recovery was reduced in the range of 18% LC to 21.6% LC, possibly reflecting to lower recovery of liquid (1.1 to 1.5 mL). The resulting liquids were viscous compared to water. With limited concentrations of oxycodone and high viscosity, these solutions might not be suitable for intravenous abuse.
The recovery of oxycodone from crushed OxyContin reached a maximum of 47.0% LC (18.8 mg) at 2 minutes of extraction in 10 mL water at 90°C-95°C, with recovery of 5.8 mL (58% of 5 mL) of liquid. The viscosity of the solution was higher than that of water. The resulting solution, having a low oxycodone concentration of 3.2 mg/mL and high viscosity, would likely not be suitable for intravenous administration. Steps taken to increase concentration by removing water, might be expected to further increase the viscosity of the solution, there raising the question of suitability for intravenous injection.

Using crushed Roxicodone, 88.3% LC and 94.7% LC of oxycodone was recovered within 0.5 minutes (only time point used), using 5 mL and 10 mL of water at 90°C-95°C, respectively. Greater than 95% of the liquid was also recovered with a viscosity similar to water. Due to the limited concentrations of oxycodone in these solutions, to be suitable for intravenous abuse, either multiple milliliters would have to be injected or the solutions would have to be concentrated by loss of water.

Study 5. Small Volume Extraction (for IV Injection) – Microwave Pretreatment of Ground 40 mg Xtampza ER Capsule Microspheres and Fine Grated OxyContin 40 mg Tablets.

Crushed Xtampza ER microspheres (mortar and pestle, 2 minutes) and crushed OxyContin (fine grater) were microwaved for 8 minutes at maximum powder using a 1200 watt microwave. Following cooling, ground material of each produce were exposed to 5 mL of water at 90°C-95°C for periods out to 15 minutes. Both the recovery of oxycodone and of liquid were documented.

Solutions suitable for intravenous injection could not be made under the conditions of the study by use of crushed microwaved (8 minutes, maximum of 1200 watts) Xtampza microspheres. Maximum oxycodone recovered was only 7.5% LC (3.0 mg) at 15 minutes of extraction in 5 mL of water at 90°C-95°C. Greater than 90% of liquid was recovered with a viscosity similar to water.

Exposure of microwaved, crushed OxyContin OP to 5 mL of water at 90°C-95°C for 15 minutes resulted in recovery of 82.9% LC (33.2 mg) of oxycodone. The liquid recovered was 4.7 mL having a viscosity a little above that of water. The resulting solution had an oxycodone concentration of 7.1 mg/mL. Intravenous injection of 1.5 mL or 2 mL of this solution might be expected to produce drug liking, and therefore have a potential by intravenous injection. It is also possible that some water could be removed thereby increasing the oxycodone concentration for purposes of intravenous abuse. How the removal of water would affect the viscosity of the resulting solution is not known.

Study 6. Dissolution Following Soaking in Beverages

In dissolution studies, the extended release properties for oxycodone from microspheres from 40 mg Xtampza capsules was not affected by prior soaking of the microspheres for 10 minutes in 30 mL of Gatorade, Dasani (water), Cranberry Juice, Coca-Cola, Rockstar, 40% ethanol, or vinegar.

Study 7. Solvent Extraction Studies. Part 1. – 40 mg Intact Xtamzpa Capsule Contents (Microspheres), Intact 30 mg Roxicodone, and Intact 40 mg OxyContin OP Tablets – Extraction with 30 mL of Ingestible Solvents at Room Temperature.

Ingestible solvents at room temperature used in extraction studies included water, 3% sodium bicarbonate, Coca-Cola, 40% ethanol, vinegar, and water at pH 4.9. Extraction times included 15
minutes, and 1, 2, 4, 8, and 24 hours. Olive oil was not an effective solvent (<6% LC extracted) for extraction of oxycodone from any of the intact products.

Intact Roxicodone tablets exhibited ≥74% LC oxycodone extracted using all solvents except olive oil.

Two hour extraction using deionized water, Coke, or vinegar, resulted in 1.0% to 1.9% LC oxycodone extracted from intact Xtampza ER and 23% to 29% LC from intact OxyContin tablets. Highest recovery of oxycodone from intact Xtampza microspheres was achieved with 40% ethanol (26.8% LC) as compared to 17.0% LC from OxyContin tablets. Intact Xtampza microspheres maintained controlled release properties for all solvents with the exception of 40% ethanol.

Study 7. Solvent Extraction Studies. Part 2. 40 mg Crushed Xtampza ER Capsule Contents (Microspheres), Crushed 30 mg Roxicodone and Crushed 40 mg OxyContin OP Tablets – Extraction with 30 mL Ingestible Solvents at Room Temperatures.

Ingestible solvents were the same as those identified in Study 7 Part 1.

The controlled release mechanism for oxycodone associated with Xtampza ER microspheres was much less affected by crushing than was the controlled release mechanism of oxycodone from OxyContin OP tablets.

Greater than 75% LC of oxycodone was recovered from crushed Roxicodone tablets within 15 minutes in all ingestible solvents except olive oil.

Whereas in deionized water (neutral pH) at room temperature under intermittent shaking, 1.4% LC and 2.7% LC of oxycodone was recovered from crushed Xtampza ER microspheres at 0.25 and 1 hours of extraction, the recovery of oxycodone was 52.1% and 67.9% under the same conditions from crushed OxyContin OP tablets. With increased agitation the recovery of oxycodone from crushed OxyContin tablets further increased to 76.8% LC and 84.8% LC at 0.25 and 1 hours, respectively. By contrast solvent agitation had no effect on recovery of oxycodone from crushed Xtampza ER microspheres (2.2% LC at 0.25 hours and 4.0% LC at 1 hour).

Under conditions of agitation, using either Coke, Vinegar, 40% ethanol or pH4.9 water, % LC oxycodone recovered from crushed Xtampza microspheres was less than 19% at 1 hour of extraction. In contrast with use of crushed OxyContin OP tablets exposed to the same solvents, % LC of oxycodone recovered was in the range of 75.7% to 82.3% with just 0.25 hours of extraction.

Study 7. Solvent Extraction Studies. Part 3. Crushed 40 mg Xtampza ER Microspheres), Crushed 30 mg Roxicodone and Crushed 40 mg OxyContin OP Tablets – Extraction with 30 mL Ingestible Solvents at Elevated Temperatures (37°C and 60°C)

Ingestible solvents were the same as those identified in Study 7 Part 1.

Crushed Roxicodone tablets exhibits >90% oxycodone extraction after just 15 minutes in all solvents except olive oil at both elevated temperatures (37°C and 60°C).
With use of deionized water as solvent, less than 14% LC of oxycodone was released at 1 hour from crushed Xtampza microspheres, whether held at 37°C or 60°C. By contrast, at 0.25 hours and 1.0 hours of extraction with water held at 37°C, 57.4% LC and 78.7% LC of oxycodone was recovered, respectively, from crushed OxyContin OP tablets. With water held at 60°C, recovery of oxycodone was above 80% LC within 0.25 hours.

The most efficient means to extract oxycodone from crushed Xtampza ER microspheres was use of either coke or vinegar held at 60°C. With 1 hour of extraction greater that 80% LC of oxycodone was extracted. With use of the same solvents under identical conditions, greater than 90% LC of oxycodone was extracted from OxyContin OP tablets.

With 1 hour extraction using bicarbonate, 40% ethanol, or pH 4.9 water held at 60°C, oxycodone recovery from crushed Xtampza ER microspheres was in the range of 13% LC to 50% LC. Under the same conditions, oxycodone recovery from crushed OxyContin OP tablets ranged from 53% LC to 89% LC. Lower oxycodone recovery for either product was achieved using the same solvents held at 37°C.

**Study 7. Solvent Extraction Studies. Part 4. Intact and Crushed 40 mg Xtampza ER Microspheres, 30 mg Roxicodone, and 40 mg OxyContin OP Tablets – Extraction with 30 mL of Advanced Solvents at Room Temperature.**

In this study Sponsor examined the use of “advanced solvents” to extract oxycodone from Xtampza ER microspheres and from OxyContin OP. These solvents included acetone, ethyl acetate, 1 N HCl, 1 N NaOH, methanol, isopropanol, and 95% ethanol.

With use of the organic solvents, acetone, ethyl acetate, and methanol, oxycodone recovery from intact or crushed Xtampza ER microspheres was greater than 69% LC with just 15 minutes of extraction. Methanol proved the most effective solvent with total oxycodone recovery (100% LC) from crushed Xtampza ER microspheres in 15 minutes of extraction. In contrast, intact OxyContin OP tablets, using the same organic solvents there was less than 5% LC oxycodone extracted at 15 minutes. In the case of crushed OxyContin OP tablets, extraction for 15 minutes with acetone, ethyl acetate, and methanol resulted in oxycodone recovery of 54.2% LC, 6.4% LC, and 96.6% LC, respectively.

With use of 95% ethanol for 1 hour, less than 21% LC oxycodone was extracted from intact Xtampzpa ER microspheres or from intact OxyContin tablets; however, 53.1% LC and 75.9% LC of oxycodone was extracted in 15 minutes from crushed Xtampzpa ER microspheres and crushed OxyContin OP tablets, respectively.

The solvent 1.0 N HCl was not effective in extraction of oxycodone from intact or crushed Xtampza ER microspheres or from intact OxyContin tablets. However, with this solvent, greater than 77% LC of oxycodone was recovered from crushed OxyContin tablets with 15 minutes of extraction. By contrast, 1.0 N NaOH was not an effective solvent for extraction of oxycodone from either Xtampza ER or OxyContin OP tablets, intact or crushed.

Sponsor attempted by back extract using water oxycodone recovered in the advanced solvents. In the case of intact or crushed Xtampza ER microspheres, <5% LC of oxycodone was recovered by first extracting using the advanced solvents followed by back extraction with water.
With use of crushed OxyContin OP tablets, initial extraction in either 95% ethanol, methanol, or 1.0 N HCl, followed by back extraction using water, resulted in >70% LC of oxycodone recovered. Methanol was the most effective solvent. Initial extraction with methanol followed by back extraction with water resulted in 84.2 % LC of oxycodone recovered.

**Study 8. Simulated Smoking (Vaporization) – Crushed 40 mg Xtampza ER microspheres, 40 mg OxyContin OP, and 30 mg Roxicodone.**

Simulated smoking studies were conducted on crushed samples. Xtampza ER 40 mg microspheres were crushed using a mortar and pestle. OxyContin OP 40 mg tablets were crushed using a microplane fine grater. Crushed Roxicodone was produced using a glass pestle.

Powdered samples of drug products were placed on an aluminum pan placed on a laboratory heating plate set to achieve the specified set temperature. Samples were heated at 200°C or 300°C for durations 3 minutes. Samples were heated at 250°C for of 1, 3, 5, 10, and 20 minutes. To recover as much vapor as possible, the sample pan was placed under a glass funnel connected to an Ahlin condenser. Vapors were collected on the inside of the funnel and condenser. The condensed material from the vapors as well as the residual sample material was analyzed for oxycodone. The % LC of oxycodone recovered in vapor was averaged from three replicates. The mass of each sample was determined before and after heating in order to quantify the total mass lost from the sample. The mass of inactive material released into the vapor was calculated based on the mass loss from the sample: inactive released was calculated as mg mass lost minus mg drug recovered in vapor condensate.

Heating samples of the crushed products to 200°C for 3 minutes was not effective in producing oxycodone vapors.

The average % LC of oxycodone recovered in vapor of heating the three product samples at 250°C for 5 minutes was in the range of 30.3 to 33.8, and therefore was similar. With heating of product samples at around 250°C for 10 minutes and minutes, the ranges of oxycodone recovery were as follows: 58.6% LC to 59.2% LC from Xtampza ER microspheres; 34.5% LC to 37.8% LC for Roxicodone; and 31.7% LC to 33.8% LC from OxyContin.

Under the specific conditions used in this study, it might be possible to abuse Xtampza ER Capsules by smoking.

**4. Clinical Studies**

Three category 2 studies were conducted in support of NDA 208-090. These studies are discussed below.
Category 2 Study CP-OXYDET-17

Sponsor conducted the Phase 1 study CP-OXYDET-17 entitled “An Open-Label, Randomized, Seven-Period, Crossover Study to Evaluate the Effects of Tampering on Oxycodone DETERx Compared with Oxycodone Solution.”

Study was designed as an open-labeled, randomized, active-controlled, naltrexone-blocked, crossover comparison conducted using 40 to 43 subjects (pharmacokinetic population), depending on treatment period. The primary objective of this study was to assess the safety and pharmacokinetics (PK) of Xtampza ER intact, crushed, and chewed in the fed and fasted states relative to an oxycodone solution administered in the fasted state.

Treatments were administered according to a randomization schedule with at least a 7 day washout period between treatments. Treatments included:

- Xtampza ER 40 mg Capsules Intact Fasted
- Xtampza ER 40 mg Capsules Intact Fed
- Xtampza ER 40 mg (Capsule Contents Crushed) Fasted
- Xtampza ER 40 mg (Capsule Contents Crushed) Fed
- Xtampza ER 40 mg (Capsule Contents Chewed) Fasted
- Xtampza ER 40 mg (Capsule Contents Chewed) Fed
- Oxycodone IR Solution 40 mg Fasted

For both the fed and fasted arms, subjects received one dose of the assigned treatment following an overnight fast of at least 10 hours. For the fed arms, subjects must have completed the HFHC meal prior to dosing.

To prepare Xtampza ER crushed treatment, the microspheres of a single, 40 mg Xtampza ER capsule were emptied into a ceramic mortar and ground using a pestle for 2 minutes. Previous in vitro studies demonstrated that this manipulation was most effective in producing a small particle size.

Xtampza ER 40 mg crushed treatment was administered by first placing the powder in the mouth followed by consumption of 240 mL of water. For administration of chewed Xtampza ER, subjects were instructed to pour capsule contents from a medicine cup into his/her mouth on the tongue and chew the capsule contents for 2 minutes, after which the subject was rinse and swallow with 120 mL of room temperature water.

Blood samples were taken pre-dose and a selected times out to 24 hours for Oxycodone IR solution treatment, 72.0 hours for Xtampza ER treatment under fasted conditions, and 48.0 hours for Xtampza ER treatment under fed conditions.

Pharmacokinetic parameters of interests were:
- $C_{\text{max}}$ – Maximum oxycodone plasma concentration achieved
- $T_{\text{max}}$ – Time to reach $C_{\text{max}}$
- $\text{AUC}_{\text{inf}}$ - Area under the oxycodone plasma concentration versus time curve extrapolated to infinity.
Statistical analysis was performed by sponsor. Analysis of variance (ANOVA) was performed on the ln-transformed AUC$_{\text{inf}}$ and C$_{\text{max}}$. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC$_{\text{inf}}$ and C$_{\text{max}}$. These ratios were expressed as a percentage relative to the reference (IR oxycodone) treatment. Consistent with the two one-sided tests for bioequivalence (BE), 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios fell entirely within the 80.0-125% FDA-defined limits.

Table 3. Pharmacokinetic Parameters for Oxycodone in Plasma Following Treatments under Fasted and Fed Conditions with Xtampza ER 40 mg (Intact, Crushed, or Chewed) and 40 mg Oxycodone IR Solution Under Fasted Conditions. (Source: Table 7 on page 58 of the Clinical Study Report (Final) for Protocol CP-OXYDET-17)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>C$_{\text{max}}$ (ng/mL) Mean (SD)</th>
<th>T$_{\text{max}}$ (hrs) Median (Range)</th>
<th>AUC$_{\text{inf}}$ Hr*ng/mL Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xtampza ER 40 mg, Intact, Fasted</td>
<td>30.7 (7.09)</td>
<td>3.00 (1.00-5.00)</td>
<td>369 (89.5)</td>
</tr>
<tr>
<td>Xtampza ER 40 mg, Intact, Fed</td>
<td>62.3 (13.0)</td>
<td>4.00 (1.50-6.00)</td>
<td>561 (124)</td>
</tr>
<tr>
<td>Xtampza ER 40 mg, Crushed, Fasted</td>
<td>34.0 (9.93)</td>
<td>3.00 (1.00-8.00)</td>
<td>410 (129)</td>
</tr>
<tr>
<td>Xtampza ER 40 mg, Crushed, Fed</td>
<td>57.6 (12.6)</td>
<td>4.50 (2.50-6.00)</td>
<td>553 (134)</td>
</tr>
<tr>
<td>Xtampza ER 40 mg, Chewed, Fasted</td>
<td>41.1 (15.2)</td>
<td>2.50 (0.50-4.50)</td>
<td>422 (113)</td>
</tr>
<tr>
<td>Xtampza ER 40 mg, Chewed, Fed</td>
<td>55.6 (10.9)</td>
<td>4.50 (2.50-8.00)</td>
<td>559 (113)</td>
</tr>
<tr>
<td>40 mg Oxycodone IR Solution Fasted</td>
<td>115 (27.3)</td>
<td>0.75 (0.50-2.00)</td>
<td>489 (80.2)</td>
</tr>
</tbody>
</table>

The results of study are showed in Table 3. Statistical analysis conducted by sponsor revealed the following results:

- Under fasted conditions, Xtampza ER 40 mg given orally whether intact, crushed, or chewed resulted in similar oxycodone C$_{\text{max}}$, T$_{\text{max}}$, and total oxycodone exposure (AUC$_{\text{inf}}$). The oxycodone C$_{\text{max}}$ for these treatments (30.7 to 41.1 ng/mL) were significantly lower than the oxycodone C$_{\text{max}}$ (115 ng/mL) produced by 40 mg oxycodone IR solution and with a longer T$_{\text{max}}$.
- Under fed conditions, Xtampza ER 40 mg given orally whether intact, crushed, or chewed resulted in similar C$_{\text{max}}$, T$_{\text{max}}$, and total oxycodone exposure (AUC$_{\text{inf}}$). The oxycodone C$_{\text{max}}$ for these treatments (ranging from 55.6 to 62.3 ng/mL) were significantly lower than the oxycodone C$_{\text{max}}$ (115 ng/mL) produced by 40 mg oxycodone IR solution and with a longer T$_{\text{max}}$.
- Regardless of whether administration is of the intact, crushed, or chewed Xtampza ER 40 mg, administration under fed conditions, compared to under fasted conditions, results in a greater oxycodone C$_{\text{max}}$ and greater total oxycodone exposure (AUC$_{\text{inf}}$), thereby suggesting a food effect with regard to oxycodone bioavailability.
Category 2 Study CP-OXYDET-19

In support of NDA 208-090 Sponsor conducted Phase 1 study CP-OXYDET-19 entitled “An Assessment of the Safety and Pharmacokinetics of Intranasal (“Snorted”) Administration of Crushed Oxycodone DETERx 40 mg, Oral Administration of Intact Oxycodone DETERx 40 mg Capsules, and Intranasal Administration of Oxycodone Powder 40 mg.”

The primary objective of this study was to compare the safety and pharmacokinetics (PK) of crushed Xtampza ER Capsules following intranasal (IN) administration, intact Xtampza ER Capsules following per oral administration, and oxycodone powder following IN administration.

Study CP-OXYDET-19 was an open-label, randomized, active-controlled, naltrexone-blocked, crossover study utilizing 13 subjects with a history of insufflating opioids recreationally and having insufflated within the last year prior to the Screening Visit.

Subjects were randomly assigned to receive 3 treatments under fed conditions (HFHC meal) with at least 7 day washout period between treatments. Treatments included:

- Crushed Xtampza ER 40 mg Intranasal
- Intact Xtampza ER 40 mg Oral
- Oxycodone Powder 40 mg Intranasal

Xtampza ER 40 mg microspheres were crushed using a mortar and pestle for 2 minutes.

Crushed microspheres from a single 40-mg Xtampza ER capsule were poured into a clean scintillation vial (held by a site staff member), which was placed on black construction paper taped to the counter, and insufflated through 1 naris using a short black straw (held by the subject) as rapidly as possible, but within a maximum of 4 minutes. Study staff performed a visual nasal cavity check once the entire dose of study drug had been insufflated. Oral Xtampza ER 40 mg was taken with 240 of water.

During treatment periods blood samples were taken pre-dose and periodically post-dose out of 48 hours for purposes of oxycodone pharmacokinetic assessment.

Pharmacokinetic parameters of interest for oxycodone in plasma included $C_{\text{max}}$, $T_{\text{max}}$, and $AUC_{\text{inf}}$.

Statistical analysis was performed by sponsor. Analysis of variance (ANOVA) was performed on the ln-transformed $AUC_{\text{inf}}$ and $C_{\text{max}}$. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed $AUC_{\text{inf}}$ and $C_{\text{max}}$. These ratios were expressed as a percentage relative to the reference (IR oxycodone) treatment. Consistent with the two one-sided tests for bioequivalence (BE), 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios fell entirely within the 80.0-125% FDA-defined limits.
Pharmacokinetic parameters for plasma oxycodone as a function of treatment are shown in Table 4 below.

Table 4. Pharmacokinetic Parameters for Oxycodone in Plasma Following Treatments with Xtampza ER 40 mg Crushed Intranasally (IN), 40 mg Xtampza ER Intact Oral, and 40 mg Oxycodone Powder Intranasally Under Fed Conditions. (N=13 Subjects) (Source: Table 8 on page 57 of the Clinical Study Report for Protocol CP-OXYDET-19)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Oxycodone C\text{max} (ng/mL) Mean (SD)</th>
<th>Oxycodone T\text{max} (Hrs) Median (Range)</th>
<th>Oxycodone AUC\text{inf} Hr*ng/mL Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushed 40 mg Xtampza ER IN</td>
<td>38.1 (6.89)</td>
<td>5.00 (1.50-8.00)</td>
<td>472 (151)</td>
</tr>
<tr>
<td>Intact 40 mg Xtampza ER Oral</td>
<td>47.5 (7.89)</td>
<td>5.03 (4.00-10.00)</td>
<td>499 (110)</td>
</tr>
<tr>
<td>40 mg Oxycodone Powder IN</td>
<td>63.9 (10.6)</td>
<td>3.00 (0.33-4.50)</td>
<td>520 (115)</td>
</tr>
</tbody>
</table>

Statistical analysis conducted by sponsor revealed the following results:

- Intranasal 40 mg oxycodone powder produced an oxycodone C\text{max} that was significantly higher than the oxycodone C\text{max} produced following either intranasal crushed 40 mg Xtampza ER or oral intact 40 mg Xtampza ER. The T\text{max} following intranasal 40 mg oxycodone powder as significantly shorter than the T\text{max} produced by the other two treatments.
- Oxycodone C\text{max} following crushed 40 mg Xtampza ER intranasal was significantly lower than the oxycodone C\text{max} achieved following oral 40 mg Xtampza ER. For both treatments there was a similar T\text{max}.
- All three treatments were bioequivalent with respect to total oxycodone exposure as revealed by the AUC\text{inf}.

The pharmacokinetic findings of this study suggest that Xtampza ER capsules may provide resistance to attempted intranasal abuse.

**Category 2 Study CP-OXYDET-25**

In support of NDA 208-090 Sponsor conducted Phase 1 study CP-OXYDET-25 entitled “An Evaluation of the Effect of Tampering on Oxycodone DETERx Compared with OxyContin.”

The primary objective of this study was to assess the safety and pharmacokinetics (PK) of intact and crushed Xtampza ER 40 mg in the fed state relative to a marketed intact and crushed oxycodone extended-release formulation (OxyContin 40 mg) in the fed state and a crushed immediate-release (IR) formulation in the fed state.

Study CP-OXYDET-25 is an open-label, randomized, 5-treatment, 5-period, active-controlled, cross-over comparison study conducted on naltrexone blockade.
Under a randomization schedule, subjects were randomly assigned to receive treatments following a high fat, high calorie meal 30 minutes prior to treatment. There was a washout period of at least 5 days between each dose of study drug. The five oral treatments included:

- Xtampza ER 40 mg (capsule intact)
- Xtampza ER 40 mg (capsule contents crushed)
- OxyContin 40 mg (tablet intact)
- OxyContin 40 mg (tablet crushed)
- IR Oxycodone 40 mg (tablet crushed)

All treatments were administered orally with 240mL of water. For preparation of crushed treatments, Xtampza ER capsule contents and IR oxycodone tablets were crushed with a ceramic mortar & pestle and OxyContin tablets was crushed with a fine grater. The crushing procedures utilized in this study were previously established as the most aggressive methods of reducing the particle size of the respective products (and thus increasing the release rates in vitro).

During treatment periods blood samples were taken pre-dose and periodically post-dose for purposes of oxycodone pharmacokinetic assessment. During periods involving either Xtampza ER or OxyContin, samples were collected out to 36 hours. During periods involving IR oxycodone, samples were taken out to 24 hours.

Pharmacokinetic parameters of interests were $C_{\text{max}}$, $T_{\text{max}}$, and $AUC_{\text{inf}}$.

Statistical analysis was performed by sponsor. Analysis of variance (ANOVA) was performed on the ln-transformed $AUC_{\text{inf}}$ and $C_{\text{max}}$. The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed $AUC_{\text{inf}}$ and $C_{\text{max}}$. These ratios were expressed as a percentage relative to the reference (IR oxycodone) treatment. Consistent with the two one-sided tests for bioequivalence (BE), 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios fell entirely within the 80.0-125% FDA-defined limits.

PK population consisted of:
- 40 subjects – treatments intact OxyContin and Crushed IR Oxycodone
- 39 subjects – treatment crushed OxyContin
- 38 subjects – treatments intact Xtampza ER and crushed Xtampza ER.

Results for $C_{\text{max}}$, $T_{\text{max}}$, and $AUC_{\text{inf}}$ for plasma oxycodone as a function of treatment are shown in Table 5 below.
Table 5. Pharmacokinetic Parameters for Oxycodone in Plasma Following Treatments under Fed Conditions with Xtampza ER 40 mg (Intact and Crushed), OxyContin OP 40 mg (Intact and Crushed), and Crushed IR Oxycodone 40 mg. (Source: Table 8 on page 58 of the Clinical Study Report for Protocol CP-OXYDET-25)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$T_{\text{max}}$ (hrs)</th>
<th>$AUC_{\text{inf}}$ Hr*ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushed IR Oxycodone 40 mg</td>
<td>79.4 (17.1)</td>
<td>1.75 (0.5-4.0)</td>
<td>561 (146)</td>
</tr>
<tr>
<td>Crushed Xtampza ER 40 mg</td>
<td>62.9 (12.6)</td>
<td>4.00 (2.0-7.0)</td>
<td>597 (149)</td>
</tr>
<tr>
<td>Crushed OxyContin 40 mg</td>
<td>78.4 (12.9)</td>
<td>1.75 (0.5-5.0)</td>
<td>587 (132)</td>
</tr>
<tr>
<td>Intact Xtampza ER 40 mg</td>
<td>67.5 (17.6)</td>
<td>3.50 (1.25-6.0)</td>
<td>581 (138)</td>
</tr>
<tr>
<td>Intact OxyContin 40 mg</td>
<td>64.9 (13.8)</td>
<td>5.00 (92.0-10.0)</td>
<td>611 (145)</td>
</tr>
</tbody>
</table>

In tests of bioequivalence conducted by sponsor the following results were found.

- Oxycodone $C_{\text{max}}$ for crushed Xtampza ER 40 mg was significantly lower than that produced by crushed IR oxycodone. Bioequivalence was established for total oxycodone exposure ($AUC_{\text{inf}}$).
- Oxycodone $C_{\text{max}}$ and total oxycodone exposure ($AUC_{\text{inf}}$) for crushed OxyContin 40 mg were bioequivalent to that produced by crushed IR oxycodone 40 mg.
- Intact Xtampza ER and Crushed Xtampza ER were bioequivalent with respect to oxycodone $C_{\text{max}}$ and $AUC_{\text{inf}}$.

The overall results of this study indicate that Xtampza ER 40 mg capsules are more resistant than OxyContin OP tablets to compromise of the controlled release of mechanism for oxycodone when each formulation is crushed. These pharmacokinetic results are in line with the in vitro extraction studies demonstrating a greater resistance to oxycodone dose dumping in water exhibited by Xtampza ER microspheres compared to OxyContin OP tablets, when each is crushed.

4.1 Human abuse potential studies

In support of NDA 208-090, Sponsor submitted the following two category 3 human abuse liability studies:

- CP-OXYDET-24 entitled “Assessment of the Oral Human Abuse Potential of Oxycodone DETERx.” Study was conducted between January 2014 and June 2014 at CRI Lifetree/PRA Health Sciences, Salt Lake City, Utah. Final report was dated November 5, 2014.
- CP-OXYDET-21 entitled “Assessment of the Relative Human Abuse Potential of Intranasal Oxycodone DETERx.” Study was conducted between October 2013 and December 2013 at CRI Lifetree/PRA Health Sciences, Salt Lake City, Utah. Final report was dated September 29, 2014.

In response to a consult request from CSS dated January 8, 2015, the Office of Biostatistics conducted a statistical review for intranasal study CP-OXYDET-21 (DARRTS, NDA 208-090, August 21, 2015, Author: Anna Sun, Ph.D.) and oral study CP-OXYDET-24 (DARRTS, NDA 208-090, June 2, 2015, Author: Anna Sun, Ph.D.).
Oral Study CP-OXYDET-24

Study CP-OXYDET-24 was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period, crossover study. The study included a Screening Phase, Drug Discrimination Phase, Treatment Phase, and Follow-up Phase. As part of the Drug Discrimination Phase, subjects were subjected to Naloxone Challenge Test to ensure they were not physically dependent upon opioids.

The primary objective of this study was to evaluate the abuse potential and PK of Xtampza ER capsules 40 mg intact in the fed state, Xtampza ER capsules 40 mg intact in the fasted state, Xtampza ER capsules 40 mg chewed in the fed state, Xtampza ER capsules 40 mg chewed in the fasted state, and IR Oxycodone 40 mg crushed in the fasted state.

Subjects were non-dependent, recreational opioid users. A recreational opioid user is defined as a user of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Phase (Visit 1). Non-dependency and tolerance to opioids was based on DSM-IV-RT criteria and naloxone challenge.

Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a two-way crossover, 1:1 ratio, double-blind, randomized design, subjects received under fasted conditions a single, oral dose of the following treatments:

- IR Oxycodone HCl 20 mg Dosed Orally Crushed, in Solution
- Placebo Dosed Orally Crushed, in Solution

Both doses were administered under fasted conditions. Subjects received either crushed oxycodone IR 20 mg or placebo mixed in solution. Immediately prior to dosing, the dosing staff swirled the study drug (with denatonim benzoate added to create a 1 ppm solution for blinding purposes) or placebo (with denatonim benzoate 1 ppm solution with microcrystalline cellulose added for blinding) solution in the dosing container for approximately 10 seconds. Subjects were instructed to drink the entire 50 mL of study drug/placebo directly from the dosing container followed by 2 separate rinses of 100 mL of room temperature, non-carbonated water. Site staff performed a thorough mouth check after each test dose had been taken. Each dose was separated by at least 24 hours.

In order to participate in the Treatment Phase, subjects were required to satisfy the following criteria in the Drug Discrimination Phase:

- A minimum $E_{\text{max}}$ of 65 points for Drug Liking VAS in response to active treatment;
- A $\geq 15$-point (Drug Liking VAS) difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
- A placebo response $\geq 40$ and $\leq 60$ points for Drug Liking VAS during the first 2 hours following drug administration
- Must be able to tolerate to study treatments in the Drug Discrimination Test as evidenced by no emesis within first 6 hours after dosing.
- Must have acceptable response to other study assessments and have ability to successfully complete the study as judged by the Investigator with input from the Sponsor.
During the Double-blind Treatment Phase, subjects were randomized, using a 6 x 6 Williams square randomization design, in a 1:1:1:1:1:1 ratio to receive a single dose of 6 treatments in a double-blind, triple-dummy design. Each treatment was separated by a minimum of 5 days. Fed doses were administered following a “high fat high calorie” (HFHC) meal. Fasting doses were administered following an overnight fast lasting at least 10 hours. Subjects received assigned dosages once in the morning. Treatments administered are shown in Table 6.

Table 6. Treatments Administered during the Treatment Phase. (Source: Table on page 10 of Clinical Study Report for Protocol CP-OXYDET-24)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chewed Capsule Contents</th>
<th>Intact Capsules</th>
<th>IR Solution</th>
<th>Fed/Fasted</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Xtampza ER Placebo</td>
<td>Xtampza ER 40 mg</td>
<td>Placebo</td>
<td>Fed</td>
</tr>
<tr>
<td>B</td>
<td>Xtampza ER Placebo</td>
<td>Xtampza ER 40 mg</td>
<td>Placebo</td>
<td>Fasted</td>
</tr>
<tr>
<td>C</td>
<td>Xtampza ER 40 mg</td>
<td>Xtampza ER Placebo</td>
<td>Placebo</td>
<td>Fed</td>
</tr>
<tr>
<td>D</td>
<td>Xtampza ER 40 mg</td>
<td>Xtampza ER Placebo</td>
<td>Placebo</td>
<td>Fasted</td>
</tr>
<tr>
<td>E</td>
<td>Xtampza ER Placebo</td>
<td>Xtampza ER Placebo</td>
<td>IR Oxycodone HCl 40 mg</td>
<td>Fasted</td>
</tr>
<tr>
<td>F</td>
<td>Xtampza ER Placebo</td>
<td>Xtampza ER Placebo</td>
<td>Placebo</td>
<td>FED</td>
</tr>
</tbody>
</table>

For the crushed IR oxycodone 40 mg in solution treatment in the Double-blind Treatment Phase, two 20 mg tablets of IR oxycodone were used.

During dosage administration, subjects were blindfolded. In the case of intact Xtampza ER treatments (active or placebo), subjects were instructed to swallow the capsules intact from the dosing containing. Swallowing was assisted with 50 mL of either oxycodone IR solution (room temperature, non-carbonated water with denatonium benzoate added to create a 1ppm solution for blinding purposes) or placebo solution (room temperature, non-carbonated water with denatonium benzoate added to create a 1ppm solution of microcrystalline cellulose added for blinding purposes. Following dosing, staff checked to ensure that capsules and solution were entirely ingested. This was followed by two additional 50 mL rinses at room temperature with non-carbonated water.

For chewed active or placebo Xtampza ER, capsule contents (beads) were poured into a small dosing cup. Subjects were instructed to pour contents from the cup onto their tongues. Next, subjects were instructed to chew the contents for 2 minutes without swallowing or talking. At the end of the 2 minutes of chewing subjects were given 50 mL of water to rinse mouth followed by swallowing. After a mouth check by study staff, subjects were given an additional 50 mL of water for another rinsing. Study staff documented the chew time, completion of the visual cavity inspection procedure, and consumption of the study drug.

During each Treatment Period of the Double-blind Treatment Phase, serial 3 mL blood samples for pharmacokinetic evaluation were collected pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours post dose.

For purposes of this review, the PK parameters determined and reviewed for oxycodone were:

- $C_{\text{max}}$ = Maximum plasma level of oxycodone achieved
- $T_{\text{max}}$ = Time to achieve $C_{\text{max}}$
• \( AUC_{\text{inf}} \) = Area under the plasma oxycodone concentration versus time curve from time 0 extrapolated to infinity.

For purposes of this review, the pharmacodynamic (PD) measures included:
• Primary measure of bipolar Drug Liking VAS
• Secondary measure of unipolar High VAS
• Secondary measure of bipolar Take Drug Again VAS
• Secondary measure of Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI/MBG) (Euphoria Effect)

Drug Liking VAS, High VAS, and ARCI/MBG scales were conducted at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. ARCI/MBG was also conducted pre-dose. Bipolar Take Drug Again VAS was conducted at 8 hours and 24 hours post-dosing.

PD endpoints included:
• \( E_{\text{max}} \) = Maximum observed effect
• \( T_{E_{\text{max}}} \) = Time to Achieve \( E_{\text{max}} \)
• \( AUE_{0-2\text{hrs}} \) = Area under the effect curve from 0 hours to 2 hours post-dosing.

Results – Subject Disposition

A total of 111 subjects participated in a naloxone challenge test of which 110 passed the test. Of these subjects 3 withdrew consent prior to entering the Drug Discrimination test. Of 107 subjects who entered the Drug Discrimination test, 64 subjects passed and entered the Treatment Phase. Forty-three subjects withdrew during or after the drug discrimination test for the following reasons: 7 subjects withdrew consent; 2 subjects had protocol deviations; 3 subjects withdrew due to emesis (adverse events); 24 subjects failed Drug Discrimination test; and 7 subjects failed Drug Discrimination based on finding of Sponsor. Sixty-three subjects received at least 1 treatment during Double-blind Treatment Phase which 38 subjects completed the double-blind Treatment Phase, receiving all treatments. During the double blind Treatment Phase, 25 subjects withdrew for the following reasons: 8 subjects for protocol deviations; 7 subjects withdrew consent; 9 subjects for adverse events (7 for emesis, 1 for irritability, and 1 for toothache); 1 subject for study drug error.

The pharmacodynamic population (PD) (38 subjects) included subjects that completed all 6 Treatment Periods with at least one PD assessment in each Treatment Period of the Double-blind Treatment Phase. This was the primary population for the PD analyses.

The pharmacokinetic population (47 subjects) consisted of subjects who completed at least 2 active Treatment Periods, who had sufficient quantifiable plasma concentration data to provide \( C_{\text{max}} \) and \( AUC \) data, and who did not experience emesis within 12 hours of dosing for Oxycodone DETERx or within 2 x median \( T_{\text{max}} \) (2x 1.07 = 2.14 h) of dosing for IR oxycodone.
Results – Pharmacokinetics of Plasma Oxycodone Following Active Treatments.

Descriptive statistics for the pharmacokinetics of oxycodone in plasma following dosing during the Treatment Phase are shown in Table 7. For purposes of conducting bioequivalence comparisons, Sponsor determined least squares means, least squares mean ratios and 90% confidence intervals for the selected pharmacokinetic parameters.

Table 7. Descriptive Statistics of Plasma Oxycodone Pharmacokinetic Parameters (All numbers except those for $T_{\text{max}}$ are arithmetic mean (SD). Values of $T_{\text{max}}$ are expressed as the median (range). (Source: Table 56 on page 169 of the Clinical Study Report for Protocol CP-OXYDET-24)

<table>
<thead>
<tr>
<th>Oxycodone PK Parameter</th>
<th>Statistic</th>
<th>Xtampza ER 40 mg</th>
<th>Xtampza ER 40 mg</th>
<th>Xtampza ER 40 mg</th>
<th>Xtampza ER 40 mg</th>
<th>IR Oxycodone 40 mg Crushed Solution Fasted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intact Fed</td>
<td>Intact Fasted</td>
<td>Chewed Fasted</td>
<td>Chewed Fasted</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>Mean (SD)</td>
<td>41.9 (12.4)</td>
<td>30.9 (9.91)</td>
<td>40.3 (12.2)</td>
<td>35.5 (12.5)</td>
<td>77.7 (24.5)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>Median (Range)</td>
<td>5.12 (1.6 – 12.1)</td>
<td>4.08 (1.57 – 8.08)</td>
<td>5.07 (2.05 – 12.10)</td>
<td>3.07 (1.07 – 6.17)</td>
<td>1.08 (0.17 – 5.10)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-3\text{hrs}}$ (h·ng/mL)</td>
<td>Mean (SD)</td>
<td>5.29 (7.37)</td>
<td>17.48 (8.80)</td>
<td>19.54 (13.88)</td>
<td>33.98 (17.56)</td>
<td>111.58 (36.79)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (h·ng/mL)</td>
<td>Mean (SD)</td>
<td>553 (131)</td>
<td>469 (107)</td>
<td>515 (122)</td>
<td>467 (126)</td>
<td>467 (106)</td>
</tr>
</tbody>
</table>

Xtampza ER 40 mg administered intact or chewed under fasted or fed conditions produced mean peak plasma oxycodone levels ($C_{\text{max}}$) that were significantly lower and appeared significantly later ($T_{\text{max}}$) than that produced by IR Oxycodone 40 mg solution fasted indicating a lack of bioequivalence. The $\text{AUC}_{0-3\text{hrs}}$ associated with IR Oxycodone 40 mg solution fasted was also significantly higher than that produced by the Xtampza ER 40 mg treatments.

With respect to oxycodone plasma $C_{\text{max}}$, bioequivalence was achieved for the treatment comparisons of chewed fasted Xtampza ER vs chewed fed Xtampza ER, chewed fasted Xtampza ER vs intact fasted Xtampza ER, chewed fasted Xtampza ER vs intact fed Xtampza ER, and chewed fed Xtampza ER vs intact fed Xtampza ER.

In terms of $\text{AUC}_{0-\text{inf}}$, representing total oxycodone plasma exposure, all treatments were bioequivalent. There was a tendency, however, for higher $\text{AUC}_{0-\text{inf}}$ for Xtampza ER under fed conditions (range of 515 to 553 h·ng/h) compared to Xtampza ER or IR Oxycodone, both under fasted conditions (rage of 467-469 h·ng/h)

Results - Pharmacodynamics

This review will focus on $E_{\text{max}}$ for the primary measure of Drug Liking VAS and for the secondary measures of High VAS and Take Drug Again VAS. The secondary measure of the ARCI/MBG scale is also included in this review because the Sponsor is proposing to place into Section 9.2 of the label information regarding the results of the ARCI/MBG scale.
This review will use the statistical review of Study CP-OXYDET-24 conducted by the CDER Office of Biostatistics (DARRTS, NDA 208-090, June 2, 2015, Author: Anna Sun, Ph.D.). This report provides descriptive statistics, statistical analysis, and percentage reduction for $E_{\text{max}}$ from the Drug Liking VAS, High VAS, Take Drug Again VAS, and the ARCI/MBG scale.

**Results – Drug Liking VAS**

For assessing Drug Liking, subjects were asked the question “Do you like the effect that you are feeling now?” The question was scored using a 0-100 mm bipolar VAS anchored on the left with “strong disliking” (score of 0); “neither like nor dislike” (score of 50) in the middle; and anchored on the right with “strong liking” (score of 100).

Descriptive statistics and statistical analysis of $E_{\text{max}}$ for Drug Liking VAS are shown in Tables 8 and 9, respectively.

Table 8. Descriptive Statistics for $E_{\text{max}}$ of Drug Liking VAS in the PD Population (N=38). (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean $E_{\text{max}}$</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>First Quartile</th>
<th>Median</th>
<th>Third Quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Intact Xtampza ER 40mg Fed</td>
<td>68.61</td>
<td>13.14</td>
<td>50.00</td>
<td>55.00</td>
<td>70.00</td>
<td>78.00</td>
<td>93.00</td>
</tr>
<tr>
<td>B: Intact Xtampza ER 40mg Fasted</td>
<td>68.79</td>
<td>13.01</td>
<td>50.00</td>
<td>55.00</td>
<td>72.00</td>
<td>78.00</td>
<td>89.00</td>
</tr>
<tr>
<td>C: Chewed Xtampza ER 40mg Fed</td>
<td>70.76</td>
<td>11.45</td>
<td>50.00</td>
<td>63.00</td>
<td>70.00</td>
<td>79.00</td>
<td>90.00</td>
</tr>
<tr>
<td>D: Chewed Xtampza ER 40mg Fasted</td>
<td>73.45</td>
<td>13.90</td>
<td>50.00</td>
<td>62.00</td>
<td>76.00</td>
<td>82.00</td>
<td>95.00</td>
</tr>
<tr>
<td>E: Crushed IR Oxycodone 40mg Solution Fasted</td>
<td>81.76</td>
<td>11.46</td>
<td>50.00</td>
<td>74.00</td>
<td>82.50</td>
<td>91.00</td>
<td>99.00</td>
</tr>
<tr>
<td>F: Placebo</td>
<td>54.87</td>
<td>8.42</td>
<td>50.00</td>
<td>50.00</td>
<td>51.00</td>
<td>55.00</td>
<td>84.00</td>
</tr>
</tbody>
</table>

The active comparator, crushed IR oxycodone 40 mg solution, produced an $E_{\text{max}}$ of Drug Liking (LS mean of 81.56 mm) that was significantly (p<0.05) above that produced by placebo IN (LS mean of 54.70 mm), thereby validating the study with respect to Drug Liking VAS.

Chewed Xtampza ER 40 mg, whether administered under fed or fasted conditions, produced maximum drug liking (LS mean $E_{\text{max}}$ of 70.73 mm and 73.83 mm, respectively) that was statistically significantly (p<0.0007) below the maximum drug liking produced by crushed IR Oxycodone 40 mg solution fasted (LS mean $E_{\text{max}}$ of 81.56 mm) but statistically significantly (p<0.05) above that reported following placebo treatment (LS mean of $E_{\text{max}}$ of 54.70 mm). Overall the $E_{\text{max}}$ of Drug Liking (81.56) produced by crushed IR Oxycodone 40 mg solution fasted seem to be low. With the limited differences (10.83 mm and 7.73 mm) in LS mean of $E_{\text{max}}$ for Drug Liking observed between fasted or fed Xtampza versus crushed IR Oxycodone 40 mg solution, it is not clear what is the clinical significance of the study results regardless of the fact that these differences were statistically significant.
Table 9. Statistical Analysis of the Mean Difference for LS Mean $E_{\text{max}}$ for Drug Liking for Primary Differences, Food Effect Differences, and Manipulation Differences (PD Population N=38) (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>LS Mean $E_{\text{max}}$</th>
<th>Standard Error</th>
<th>Pr &gt;</th>
<th>Lower Confidence Limit</th>
<th>Upper Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Intact Xtampza ER 40 mg Fed</td>
<td>68.9368</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>65.1578</td>
<td>72.7158</td>
</tr>
<tr>
<td>B: Intact Xtampza ER 40 mg Fasted</td>
<td>69.3090</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>65.5300</td>
<td>73.0880</td>
</tr>
<tr>
<td>C: Chewed Xtampza ER 40 mg Fed</td>
<td>70.7275</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>66.9486</td>
<td>74.5065</td>
</tr>
<tr>
<td>D: Chewed Xtampza ER 40 mg Fasted</td>
<td>73.8299</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>70.0509</td>
<td>77.6089</td>
</tr>
<tr>
<td>E: Crushed IR Oxycodone 40 mg in Solution Fasted</td>
<td>81.5629</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>77.7839</td>
<td>85.3419</td>
</tr>
<tr>
<td>F: Placebo</td>
<td>54.7023</td>
<td>1.9151</td>
<td>&lt;0.0001</td>
<td>50.9233</td>
<td>58.4813</td>
</tr>
</tbody>
</table>

Primary Differences

| Treatment E vs Treatment C | 10.8354                   | 2.2465         | <0.0001 | 6.4026                 | 15.2682                |
| Treatment E vs Treatment D | 7.7331                    | 2.2346         | 0.0007  | 3.3236                 | 12.1425                |

Food Effect (Difference)

| Treatment A vs. Treatment B | -0.3722                   | 2.2346         | 0.8679  | -4.7816                | 4.0372                 |
| Treatment C vs Treatment D  | -31023                    | 2.2346         | 0.1668  | -7.5117                | 1.3071                 |

Manipulation Effect (Difference)

| Treatment A vs Treatment C | -1.7907                   | 2.2465         | 0.4264  | -6.2235                | 2.6421                 |
| Treatment B vs Treatment D | -4.5208                   | 2.2465         | 0.0457  | -8.9537                | -0.08802               |

In addition, under fed conditions there was no significant difference ($p = 0.4264$) in $E_{\text{max}}$ drug liking reported following intact and chewed Xtampza ER 40 mg (LS mean of 68.94 mm vs 70.73 mm). Under fasted conditions there was only a modest significant increase $E_{\text{max}}$ of drug liking following chewed Xtampza ER (LS mean of 73.83 mm) compared to following intact Xtampza ER administration (LS mean of 61.31 mm). So the results demonstrate that chewing of Xtampza ER whether under fed or fasted conditions produced little or no increases in maximum drug liking compared to that produced by administration of the intact, non-manipulated Xtampza ER. Collectively these studies suggest that Xtampza ER may have a deterrent effect to abuse by chewing, at least under the chewing conditions used in this study.

Comparisons across fed and fasted states indicate that there was no food effect observed regarding maximum drug liking following administration of intact Xtampza ER ($p=0.8679$) or chewed Xtampza ER 40 mg ($p=0.1668$).

Percentage Reduction – Drug Liking VAS

Table 10 provides data on the percent reduction in $E_{\text{max}}$ of Drug Liking VAS, as calculated by the CDER Office of Biostatistics, for the primary comparisons of Chewed Xtampza ER Fed (Treatment C) versus Crushed IR Oxycodone Fasted (Treatment E) and for Chewed Xtampza ER Fasted (Treatment D) versus Crushed IR Oxycodone Fasted (Treatment E)

Out of 38 total subjects, 30 (78.95%) had some reduction in $E_{\text{max}}$ of drug liking after taking chewed Xtampza ER under fed (HFHC) conditions compared to after taking crushed IR oxycodone fasted.
Eighteen subjects and 11 subjects following chewed Xtampza ER fed displayed 30% and 50% reductions, respectively, in $E_{\text{max}}$ of drug liking compared to that produced by crushed IR Oxycodone fasted.

Out of 38 total subjects, 25 (65.79%) had some reduction in $E_{\text{max}}$ of drug liking after taking chewed Xtampza ER under fed (HFHC) conditions compared to after taking crushed IR oxycodone fasted. Twelve subjects and 9 subjects following chewed Xtampza ER fasted displayed 30% and 50% reductions, respectively, in $E_{\text{max}}$ of drug liking compared to that produced by crushed IR Oxycodone fasted.

Table 10 Percentage Reduction in $E_{\text{max}}$ of Drug Liking VAS, for Chewed Xtampza ER HFHC (Trt c) vs Crushed IR Oxycodone Fasted (Trt E) and for Chewed Xtampza ER Fasted (Trt D) vs Crushed IR Oxycodone Fasted (Trt E). (Pharmacodynamic Population, N=38) (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Percentage of Reduction (%) in $E_{\text{max}}$ of Drug Liking VAS</th>
<th>Chewed Xtampza ER Fed (Trt C) Vs Crushed IR Oxycodone HCl Fasted (Trt E)</th>
<th>Chewed Xtampza ER Fasted (Trt D) Vs Crushed IR Oxycodone HCL Fasted (Trt E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Percentage of subjects (%)</td>
<td>Frequency</td>
</tr>
<tr>
<td>≥0</td>
<td>30</td>
<td>78.95</td>
</tr>
<tr>
<td>≥10</td>
<td>26</td>
<td>68.42</td>
</tr>
<tr>
<td>≥20</td>
<td>23</td>
<td>60.53</td>
</tr>
<tr>
<td>≥30</td>
<td>18</td>
<td>47.37</td>
</tr>
<tr>
<td>≥40</td>
<td>15</td>
<td>39.47</td>
</tr>
<tr>
<td>≥50</td>
<td>11</td>
<td>28.95</td>
</tr>
<tr>
<td>≥60</td>
<td>9</td>
<td>23.68</td>
</tr>
<tr>
<td>≥70</td>
<td>4</td>
<td>10.53</td>
</tr>
<tr>
<td>≥80</td>
<td>4</td>
<td>10.53</td>
</tr>
<tr>
<td>≥90</td>
<td>3</td>
<td>7.89</td>
</tr>
<tr>
<td>≥100</td>
<td>2</td>
<td>5.26</td>
</tr>
</tbody>
</table>

Results – High VAS

For assessing High VAS, subjects were asked the question “How high are you now?” Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by “none” (score of 0) and on the right by “extremely” (score of 100).

Descriptive statistics and statistical analysis of $E_{\text{max}}$ for Drug Liking VAS are shown in Tables 7 and 8, respectively.
The active comparator, crushed IR oxycodone 40 mg solution, produced an $E_{\text{max}}$ of high (LS mean of 68.32 mm) that was significantly ($p<0.05$) above that produced by placebo IN (LS mean of 9.87 mm), thereby validating the study with respect to High VAS.

Table 11. Descriptive Statistics for $E_{\text{max}}$ of High VAS in the PD Population (N=38). (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0-100 Point Unipolar High VAS (mm)</th>
<th>Mean $E_{\text{max}}$</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>First Quartile</th>
<th>Median</th>
<th>Third Quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Intact Xtampza ER 40mg Fed</td>
<td>36.00</td>
<td>26.94</td>
<td>1.00</td>
<td>10.00</td>
<td>34.50</td>
<td>54.00</td>
<td>94.00</td>
<td></td>
</tr>
<tr>
<td>B: Intact Xtampza ER 40mg Fasted</td>
<td>33.58</td>
<td>26.20</td>
<td>0.00</td>
<td>4.00</td>
<td>34.50</td>
<td>56.00</td>
<td>82.00</td>
<td></td>
</tr>
<tr>
<td>C: Chewed Xtampza ER 40mg Fed</td>
<td>37.42</td>
<td>24.44</td>
<td>1.00</td>
<td>19.00</td>
<td>33.00</td>
<td>55.00</td>
<td>89.00</td>
<td></td>
</tr>
<tr>
<td>D: Chewed Xtampza ER 40mg Fasted</td>
<td>44.68</td>
<td>29.04</td>
<td>0.00</td>
<td>21.00</td>
<td>51.50</td>
<td>66.00</td>
<td>95.00</td>
<td></td>
</tr>
<tr>
<td>E: Crushed IR Oxycodone HCl 40mg Solution Fasted</td>
<td>68.92</td>
<td>24.97</td>
<td>3.00</td>
<td>62.00</td>
<td>72.00</td>
<td>89.00</td>
<td>99.00</td>
<td></td>
</tr>
<tr>
<td>F: Placebo</td>
<td>10.26</td>
<td>19.16</td>
<td>0.00</td>
<td>1.00</td>
<td>2.00</td>
<td>5.00</td>
<td>79.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Statistical Analysis of the Mean Difference for LS Mean $E_{\text{max}}$ for High for Primary Differences, Food Effect Differences, and Manipulation Differences (PD Population N=38) (Source: CDER Office of Biostatistics)

| Unipolar High VAS | LS Mean $E_{\text{max}}$ | Standard Error | $Pr>|t|$ | Lower Confidence Limit | Upper Confidence Limit |
|-------------------|--------------------------|----------------|----------|------------------------|------------------------|
| Treatments | | | | | | |
| A: Intact Xtampza ER 40 mg Fed | 37.3172 | 4.0802 | <0.0001 | 29.2660 | 45.3684 |
| B: Intact Xtampza ER 40 mg Fasted | 34.9554 | 4.0802 | <0.0001 | 26.9042 | 43.0066 |
| C: Chewed Xtampza ER 40 mg Fed | 37.6983 | 4.0802 | <0.0001 | 29.6471 | 45.7495 |
| D: Chewed Xtampza ER 40 mg Fasted | 45.5583 | 4.0802 | <0.0001 | 37.5071 | 53.6095 |
| E: Crushed IR Oxycodone HCl 40 mg in Solution Fasted | 68.3243 | 4.0802 | <0.0001 | 60.2731 | 76.3755 |
| F: Placebo | 9.8677 | 4.0802 | <0.0001 | 1.8166 | 17.9189 |
| Primary Differences | | | | | | |
| Treatment E vs Treatment C | 30.6260 | 4.4937 | <0.0001 | 21.7588 | 39.4932 |
| Treatment E vs Treatment D | 22.7660 | 4.4700 | <0.0001 | 13.9456 | 31.5864 |
| Food Effect (Difference) | | | | | | |
| Treatment A vs. Treatment B | 2.3618 | 4.4700 | 0.5979 | -6.4586 | 11.1822 |
| Treatment C vs Treatment D | -7.8600 | 4.4700 | 0.0804 | -16.6804 | 0.9604 |
| Manipulation Effect (Difference) | | | | | | |
| Treatment A vs Treatment C | -0.3811 | 4.4937 | 0.9325 | -2.9483 | 8.4861 |
| Treatment B vs Treatment D | -10.6029 | 4.4937 | 0.0194 | -19.4701 | -1.7357 |

Chewed Xtampza ER 40 mg whether administered under fed or fasted conditions produced maximum high (LS mean $E_{\text{max}}$ of 37.70 mm and 45.56 mm, respectively) that was significantly ($p<0.0001$) below the maximum high produced by crushed IR Oxycodone 40 mg solution fasted (LS mean $E_{\text{max}}$ of 68.32 mm) but significantly ($p<0.05$) above that reported following placebo treatment (LS mean of 9.87 mm).
Under fed conditions there was no significant difference (p = 0.932) in maximum high reported following intact and chewed Xtampza ER 40 mg (LS mean of 37.32 mm vs 37.70 mm, respectively). However, under fasted conditions chewed Xtampza ER 40 mg produced a statistically significantly higher (p=0.0194) High than that produced by intact Xtampza ER 40 mg (E_{max} LS mean of 45.56 mm vs 35.00 mm).

No statistically significant food effects on E_{max} of High VAS were observed between Xtampza ER treatments (intact or chewed) under fed and fasted conditions.

Results – Take Drug Again VAS

The Take Drug Again VAS assessment involved asking subjects the question, “Would you want to take the drug you just received again, if given the opportunity?” The question was scored using a 0-100 mm bipolar VAS anchored on the left with “definitely would not” (score of 0); “do not care” (score of 50) in the middle; and anchored on the right with “definitely would” (score of 100).

Descriptive statistics and statistical analysis of E_{max} for Take Drug Again VAS are shown in Tables 9 and 10, respectively.

The active comparator, crushed IR oxycodone HCl 40 mg solution, produced an E_{max} of Take Drug Again VAS (LS mean of 74.73 mm) that was statistically significantly (p<0.05) above that produced by placebo (LS mean of 51.79 mm), thereby validating the study with respect to Take Drug Again VAS.

Table 13. Descriptive Statistics for E_{max} of Take Drug Again VAS in the PD Population (N=38).
(Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean E_{max}</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>First Quartile</th>
<th>Median</th>
<th>Third Quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Intact Xtampza ER 40mg Fed</td>
<td>70.58</td>
<td>18.12</td>
<td>26.00</td>
<td>50.00</td>
<td>74.00</td>
<td>85.00</td>
<td>99.00</td>
</tr>
<tr>
<td>B: Intact Xtampza ER 40mg Fasted</td>
<td>70.18</td>
<td>15.96</td>
<td>50.00</td>
<td>52.00</td>
<td>68.50</td>
<td>83.00</td>
<td>98.00</td>
</tr>
<tr>
<td>C: Chewed Xtampza ER 40mg Fed</td>
<td>69.26</td>
<td>18.90</td>
<td>3.00</td>
<td>57.00</td>
<td>69.00</td>
<td>84.00</td>
<td>98.00</td>
</tr>
<tr>
<td>D: Chewed Xtampza ER 40mg Fasted</td>
<td>73.74</td>
<td>14.92</td>
<td>50.00</td>
<td>63.00</td>
<td>74.00</td>
<td>87.00</td>
<td>98.00</td>
</tr>
<tr>
<td>E: Crushed IR Oxycodone HCl 40mg Solution Fasted</td>
<td>75.45</td>
<td>16.79</td>
<td>37.00</td>
<td>64.00</td>
<td>75.50</td>
<td>90.00</td>
<td>100.00</td>
</tr>
<tr>
<td>F: Placebo</td>
<td>52.66</td>
<td>13.35</td>
<td>3.00</td>
<td>50.00</td>
<td>50.00</td>
<td>50.00</td>
<td>95.00</td>
</tr>
</tbody>
</table>

LS mean E_{max} values for Take Drug Again were in the range of 68.85 mm to 74.73 mm for all active treatments under fasted and fed conditions, indicating that subjects, if given the opportunity again, would be willing to take these treatments again (See Table 9). By contrast, subjects expressed ambivalence to taking again placebo (E_{max} LS mean of 51.79 mm).
Table 14. Statistical Analysis of the Mean Difference for LS Mean $E_{\text{max}}$ for Take Drug Again VAS for Primary Differences, Food Effect Differences, and Manipulation Differences (PD Population N=38) (Source: CDER Office of Biostatistics)

| Treatments                        | $E_{\text{max}}$ LS Mean | Standard Error | Pr > |t|  | Lower Confidence Limit | Upper Confidence Limit |
|-----------------------------------|---------------------------|----------------|------|----|------------------------|------------------------|
| A: Intact Xtampza ER 40 mg Fed    | 70.4588                   | 2.6630         | $<$0.0001 | 65.2040 | 75.7136                |
| B: Intact Xtampza ER 40 mg Fasted| 70.3956                   | 2.6630         | $<$0.0001 | 65.1408 | 75.6504                |
| C: Chewed Xtampza ER 40 mg Fed   | 68.8486                   | 2.6630         | $<$0.0001 | 63.5938 | 74.1034                |
| D: Chewed Xtampza ER 40 mg Fasted| 73.6325                   | 2.6630         | $<$0.0001 | 68.3777 | 78.8872                |
| E: Crushed IR Oxycodone 40 mg in Solution Fasted | 74.7259 | 2.6630 | $<$0.0001 | 69.4711 | 79.9807 |
| F: Placebo                        | 51.7914                   | 2.6630         | $<$0.0001 | 46.5366 | 57.0462                |

Primary Differences

| Treatment E vs Treatment C       | 5.8773                    | 2.9567         | 0.0484 | 0.0492 | 11.7116                |
| Treatment E vs Treatment D       | 1.0934                    | 2.9411         | 0.7105 | -4.7101 | 6.8970                |

Food Effect (Difference)

| Treatment A vs. Treatment B      | 0.06326                   | 2.9411         | 0.9829 | -5.7403 | 5.8668                |
| Treatment C vs Treatment D       | -4.7838                   | 2.9411         | 0.1056 | -10.5874 | 1.0197               |

Manipulation Effect (Difference)

| Treatment A vs Treatment C       | 1.6102                    | 2.9567         | 0.5867 | -4.2241 | 7.4455                |
| Treatment B vs Treatment D       | -3.2369                   | 2.9567         | 0.2751 | -9.0712 | 2.5975                |

With the exception of a marginal increase in willingness to take again crushed IR Oxycodone 40 mg solution over that of taking chewed Xtampza ER under fasted conditions, statistically significant differences were not observed in LS mean $E_{\text{max}}$ values of Take Drug Again for the various treatments across fasted and fed states.

Results – ARCI/MBG Scale

The ARCI/MBG subscale is used to assess euphoria and positive mood, with each item scored on a 2-point scale (0-1), where 0 = false, 1 = true. The total score is calculated by adding the individual scores, with a possible total score of 16 for the MBG subscale (questions 1-16).

Descriptive statistics and statistical analysis of $E_{\text{max}}$ for ARCI/MBG scale are shown in Tables 11 and 12, respectively.

The active comparator, crushed IR oxycodone 40 mg solution, produced an $E_{\text{max}}$ on the ARCI/MBG scale (LS mean of 7.25) that was statistically significantly ($p<0.05$) above that produced by placebo (LS mean of 1.54), thereby validating the study with respect to the ARCI/MBG scale.
Table 15. Descriptive Statistics for ARCI/MBG Subscale in the PD Population (N=38). (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (E_{\text{max}})</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>First Quartile</th>
<th>Median</th>
<th>Third Quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Intact Xtampza ER 40mg Fed</td>
<td>4.13</td>
<td>4.80</td>
<td>0.00</td>
<td>0.00</td>
<td>2.00</td>
<td>8.00</td>
<td>14.00</td>
</tr>
<tr>
<td>B: Intact Xtampza ER 40mg Fasted</td>
<td>4.26</td>
<td>5.03</td>
<td>0.00</td>
<td>0.00</td>
<td>3.00</td>
<td>7.00</td>
<td>16.00</td>
</tr>
<tr>
<td>C: Chewed Xtampza ER 40mg Fed</td>
<td>4.03</td>
<td>4.33</td>
<td>0.00</td>
<td>0.00</td>
<td>2.50</td>
<td>7.00</td>
<td>14.00</td>
</tr>
<tr>
<td>D: Chewed Xtampza ER 40mg Fasted</td>
<td>5.05</td>
<td>4.94</td>
<td>0.00</td>
<td>0.00</td>
<td>3.50</td>
<td>8.00</td>
<td>14.00</td>
</tr>
<tr>
<td>E: Crushed IR Oxycodone HCL 40mg Solution Fasted</td>
<td>6.95</td>
<td>5.60</td>
<td>0.00</td>
<td>1.00</td>
<td>7.00</td>
<td>12.00</td>
<td>16.00</td>
</tr>
<tr>
<td>F: Placebo</td>
<td>1.37</td>
<td>2.62</td>
<td>0.00</td>
<td>0.00</td>
<td>2.00</td>
<td>14.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 16. Statistical Analysis of the Mean Difference for LS Mean \(E_{\text{max}}\) for ARCI/MBG for Primary Differences, Food Effect Differences, and Manipulation Differences (PD Population N=38) (Source: CDER Office of Biostatistics)

| 0-16 Point ARCI/MBG Scale | LS Mean \(E_{\text{max}}\) | Standard Error | Pr > |t| | Lower Confidence Limit | Upper Confidence Limit |
|---------------------------|----------------------------|----------------|-------|---|------------------------|------------------------|
| Treatments                |                           |                |       |   |                        |                        |
| A: Intact Xtampza ER 40 mg Fed | 4.3430             | 0.7406          | <0.0001 | 2.8815   | 5.8045                 |
| B: Intact Xtampza ER 40 mg Fasted | 4.5963             | 0.7397          | <0.0001 | 3.1365   | 6.0560                 |
| C: Chewed Xtampza ER 40 mg Fed | 4.3546             | 0.7406          | <0.0001 | 2.8930   | 5.8162                 |
| D: Chewed Xtampza ER 40 mg Fasted | 5.2170             | 0.7397          | <0.0001 | 3.7572   | 6.6768                 |
| E: Crushed IR Oxycodone HCl 40 mg Solution Fasted | 7.2490             | 0.7471          | <0.0001 | 5.7747   | 8.7233                 |
| F: Placebo                | 1.5379             | 0.7482          | 0.0413 | 0.06143  | 3.0144                 |

Primary Differences

| Treatment E vs Treatment C | 2.8944             | 0.7644          | 0.0002 | 1.3858   | 4.4030                 |
| Treatment E vs Treatment D | 2.0320             | 0.7587          | 0.0081 | 0.5348   | 3.5293                 |

Food Effect (Difference)

| Treatment A vs Treatment B | -0.2533            | 0.7541          | 0.7374 | -1.7414  | 1.2348                 |
| Treatment C vs Treatment D | -0.8624            | 0.7540          | 0.2543 | -2.3504  | 0.6256                 |

Manipulation Effect (Difference)

| Treatment A vs Treatment C | -0.01161           | 0.7606          | 0.9878 | -1.5127  | 1.4894                 |
| Treatment B vs Treatment D | -0.6207           | 0.7569          | 0.4133 | -2.1145  | 0.8730                 |

It is worth noting that the LS mean 7.25 for the ARCI/MBG scale obtained following IR Oxycodone HCl 40 mg in solution was low particularly considering that this scale allows a maximum response (euphoric) of 16 points. This suggests that the positive comparator is producing a limited amount of euphoria at least as measured using the ARCI/MBG scale.

Chewed Xtampza ER 40 mg whether administered under fed or fasted conditions produced maximum euphoria (LS mean \(E_{\text{max}}\) of 4.35 and 5.22, respectively) that was statistically significantly (p\leq 0.0081) below the maximum euphoria produced by crushed IR Oxycodone 40 mg solution fasted (LS mean \(E_{\text{max}}\) of 7.25) but significantly (p<0.05) above that reported following placebo treatment LS mean of \(E_{\text{max}}\).
However the differences in $E_{\text{max}}$ on the ARCI/MBG scale between chewed Xtampza ER 40 mg under fed or fasted conditions (2.89 and 2.03) verses crushed IR Oxycodone 40 mg solution were small thereby raising the issue of whether these differences are clinically significant.

Whether within the fed state (Treatment A vs Treatment C) or fasted state (Treatment B vs Treatment D), there were no differences observed between intact and chewed Xtampza ER 40 mg with respect to the maximum euphoria produced. (See Table 11)

Likewise, within the given intact (Treatment A vs Treatment B) or chewed state (Treatment C vs Treatment D), no food effects were observed with regarding to documenting euphoria. (See Table 11)

The overall study results from the ARCI/MBG scale are not sufficient to provide support for an oral abuse deterrent claim for Xtampza ER. Although chewed Xtampza ER resulted in a statistically lower $E_{\text{max}}$ on the ARCI/MBG scale compared to IR Oxycodone HCl in solution, both the lower $E_{\text{max}}$ achieved with IR Oxycodone HCl 40 mg and the small differences in $E_{\text{max}}$ between chewed Xtampza ER and IR Oxycodone make it difficult to draw conclusions regarding possible clinical significance between these treatments.

**Intranasal Human Abuse Potential Study CP-OXYDET-21**

Study CP-OXYDET-21 a randomized, double-blind, double-dummy, positive- and placebo-controlled, single-dose, 4-treatment, 4-period crossover comparison study. Study consisted of a Screening Phase, Drug Discrimination Phase, Treatment Phase, and Follow-Up Phase. As part of the Drug Discrimination Phase subjects were required to pass a Naloxone Challenge Test.

The primary objective of this study was to evaluate the abuse potential and PK of crushed Xtampza ER 40 mg following intranasal administration, intact Xtampza ER 40 mg following oral administration, and crushed IR oxycodone 40 mg following intranasal administration.

Subjects were non-dependent recreational opioid user. A recreational opioid user is defined as a user of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Phase (Visit 1). Subjects were required to have a history of intranasal (IN) drug administration of at least 3 times within the last year prior to the Screening Phase (Visit 1). Subjects could not be dependent upon opioids as determined by DSM-IV-TR criteria or by naloxone challenge.

During the Drug Discrimination Test, subjects after receiving a HFHC meal were randomized to receive each of 2 treatments in a double-blind, random order:

- Crushed IR Oxycodone HCl 20 mg Dosed IN
- Crushed Placebo Dosed IN

An interval of approximately 24 hours after the first dose of study drug/placebo in the Drug Discrimination Test provided a washout of study drug before the subjects were crossed over to the next treatment. For the crushed IR oxycodone 20 mg IN treatment used in the Drug Discrimination Phase, four 5 mg tablets of IR oxycodone were used.
In order to participate in the Treatment Phase, subjects were required to satisfy the following criteria in the Drug Discrimination Phase:

- A minimum $E_{\text{max}}$ of 65 points for Drug Liking VAS in response to active treatment;
- A $\geq 15$-point (Drug Liking VAS) difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
- A placebo response $\geq 40$ and $\leq 60$ points for Drug Liking VAS during the first 2 hours following drug administration
- Must be able to tolerate study treatments in the Drug Discrimination Test as evidenced by no emesis within first 6 hours after dosing.
- Must be able to completely insufflate the entire volume of test doses administered during Drug Discrimination Test.
- Must have acceptable response to other study assessments and have ability to successfully complete the study as judged by the Investigator with input from the Sponsor.

During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1 ratio to receive 1 of 4 treatment sequences of 4 single dose treatments in a double-blind, double-dummy design. Each treatment was separated by a minimum of 5 days. Descriptions of the treatments are provided in Table 13.

Table 17. Treatments Administered During the Treatment Phase. (Source: Table 2 on page 61 of the Clinical Study Report for Protocol CP-OXYDET-21)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intranasal (IN) Administration</th>
<th>Oral Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Xtampza ER 40 mg Crushed (420 mg) (1 x 40 mg Capsule)</td>
<td>Intact Placebo Xtampza ER</td>
</tr>
<tr>
<td>B</td>
<td>Placebo Xtampza ER Crushed (420 mg)</td>
<td>Intact 40 mg (1 x 40 mg Capsule)</td>
</tr>
<tr>
<td>C</td>
<td>IR Oxycodone HCl 40 mg Crushed (420 mg) (4 x 10 mg IR Oxycodone HCl Tablets)</td>
<td>Intact Placebo Xtampza ER</td>
</tr>
<tr>
<td>D</td>
<td>Placebo Xtampza ER Crushed (420 mg)</td>
<td>Intact Placebo Xtampza ER</td>
</tr>
</tbody>
</table>

The optimized mortar and pestle crushing procedure was supplied to the clinical site pharmacy. The individual Xtampza ER 40 mg capsule contents were crushed for 2 minutes at a speed of approximately 100 rpm using a ceramic mortar and pestle. The active comparator, oxycodone IR tablets were also crushed in the same way as described for Xtampza ER. Four 10 mg oxycodone IR tablets were crushed to obtain a 40 mg dose.

In a report entitled “CP-OXYDET-21: Post-Study Appearance and Particle Size Analysis of Nasal Treatments” Sponsor provided information on the particle size distribution of left over samples of treatments intended for study CP-OXYDET-21 Particle size distribution as determined by sieve analysis, showed that crushing oxycodone IR tablets resulted in a fine powder as evidenced by mean D50 and D90 values of 59.0 µm and 147.0 µm, respectively. By contrast, crushing the content of Xtampza ER 40 mg capsules resulted in powder with a larger particle size distribution as evidenced by mean D10, D50, and D90 values of 206.3 µm, 305.9 µm, and 457.5 µm.

Reference ID: 3817310
All doses were administered following a 20 minute HFHC meal completed in the morning. Oral study drugs were administered with 240 mL of room temperature, noncarbonated water immediately prior to administration of IN study drugs. Subjects self-administered IN study drugs, out of a scintillation vial (held by a site staff member) through a short black straw (held by the subject) over colored construction paper taped to a light box lit with black light. All study drugs were administered in a low lit room by unblinded staff members. Each dose of the assigned IN treatment was insufflated as rapidly as possible, but subjects had to finish within a maximum of 4 minutes. Subjects could use one or both nares – this was recorded in the casebook.

During each Treatment Period of the Double-blind Treatment Phase, 4 mL serial blood samples for pharmacokinetic (PK) evaluation of plasma oxycodone levels were collected pre-dose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours post-dose.

For purposes of this review, the PK parameters determined and reviewed for oxycodone were:
- \( C_{\text{max}} \) = Maximum plasma level of oxycodone achieved
- \( T_{\text{max}} \) = Time to achieve \( C_{\text{max}} \)
- \( \text{AUC}_{\text{inf}} \) = Area under the plasma oxycodone concentration versus time curve from time 0 extrapolated to infinity.

For purposes of this review, the pharmacodynamic (PD) measures included:
- Primary measure of Bipolar Drug Liking VAS
- Secondary measure of unipolar High VAS
- Secondary measure of Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI/MBG) (Euphoria Effect)
- Secondary measure of bipolar Take Drug Again VAS
- Ease of Snorting VAS
- Percentage of drug insufflated (mg %)

Drug Liking VAS, High VAS, and ARCI/MBG scales were conducted at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. ARCI/MBG was also conducted pre-dose. Take Drug Again VAS was conducted at 8 hours and 24 hours post-dose. The Ease of Snorting VAS was completed within 5 minutes following dosing.

PD endpoints included:
- \( E_{\text{max}} \) = Maximum observed effect
- \( T_{E_{\text{max}}} \) = Time to Achieve \( E_{\text{max}} \)
- \( \text{AUE}_{0-2\text{hrs}} \) = Area under the effect curve from 0 hours to 2 hours post-dosing.

A Nasal Effects assessment was completed during the Drug Discrimination Phase at predose and at 0.25, 0.5, 1.0 and 2 hours post dose and in each Treatment Period of the Double-blind Treatment Phase with IN dosing at pre-dose and at 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 12.0 hours post dose. Nasal effects assessments included an assessment of IN irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.
Results - Subject Disposition

Sixty-four subjects entered the Drug Discrimination Phase and underwent the Naloxone Challenge Test; all subjects passed the test and proceeded to the Drug Discrimination Test. Of the 64 subjects who entered the Drug Discrimination Test, 15 failed the Drug Discrimination Test, 6 experienced an adverse event (AE), i.e., emesis, which required withdrawal according to protocol mandated criteria, 3 withdrew due to subject decision and 1 was withdrawn due to a protocol violation. Of the 39 subjects who entered the Double-blind Treatment Phase, 36 completed the study. Three withdrew during the Double-blind Treatment Phase: 1 subject experienced an AE (emesis) that required withdrawal according to the protocol (Subject 1060/2035); 1 subject withdrew due to subject decision (Subject 1031/2013 withdrew due to unwillingness to consume the HCHF meal for the duration of the study); and 1 was withdrawn to Investigator decision (Subject 1049/2027 was withdrawn by the Investigator because the Medical Monitor recommended the subject be withdrawn due to receiving prescription medications to treat Acarodermatitis.

The pharmacokinetic population consisted of 36 subjects. The pharmacodynamic population also consisted of 36 subjects.

Percent of Drug Insufflated (mg %)

All intranasal doses of drug in the Qualification Phase and Treatment Phase were completely insufflated.

Ease of Snorting VAS

Ease of Snorting VAS was completed within 5 minutes of completing the intranasal administration of study drugs. This scale assessed the difficulty of snorting the study drugs. The question was scored using a 100-mm, unipolar VAS anchored on the left with “very easy (score of 0) and anchored on the right with “very difficult” (score of 100).

The least square mean (SEM) scores were 40.05 (4.49), 31.61 (4.49), and 33.53 (4.49) following intranasal treatment with Xtampza ER, IR Oxycodone HCl, and placebo, respectively. Statistical analysis conducted by Sponsor demonstrated no statistically significant differences between these treatments in the ease of snorting.

Results – Pharmacokinetics of Oxycodone in Plasma as a Function of Treatment

The PK Population (36 subjects) included subjects in the PD Population who had sufficient quantifiable plasma concentration data to provide $C_{\text{max}}$ and AUC data, and who did not experience emesis within 12 hours of dosing for Xtampza ER (intact PO and crushed IN) or within 2 x median $T_{\text{max}}$ (5 hours) of dosing for crushed IR oxycodone IN.

Descriptive statistics for selected pharmacokinetic parameters for oxycodone in plasma following treatments are found in Table 14. Statistical analysis conducted by Sponsor was based on differences in least square means and determination of 90% confidence intervals (data not shown in this review).
Table 18. Pharmacokinetic Parameters for Oxycodone in Plasma Following Active Treatments during the Treatment Phase (Pharmacokinetic Population N = 36) (Source: Table 29 on page 133 of the Clinical Study Report for Protocol CP-OXYDET-21)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Statistic</th>
<th>Crushed Xtampza ER 40 mg IN</th>
<th>Crushed IR Oxycodone HCl 40 mg IN</th>
<th>Intact Xtampza ER 40 mg Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>Mean (SD)</td>
<td>29.8 (6.58)</td>
<td>60.9 (11.9)</td>
<td>40.7 (8.87)</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (Hr)</td>
<td>Median (Range)</td>
<td>5.08 (1.58 – 12.10)</td>
<td>2.58 (0.28 – 6.05)</td>
<td>5.08 (1.58 – 8.08)</td>
</tr>
<tr>
<td>( \text{AUC}_{0-3\text{hrs}} ) (hr·ng/mL)</td>
<td>Mean (SD)</td>
<td>41.4 (16.2)</td>
<td>141 (26.4)</td>
<td>25.0 (26.1)</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (hr·ng/mL)</td>
<td>Mean (SD)</td>
<td>459 (106)</td>
<td>577 (124)</td>
<td>477 (90.5)</td>
</tr>
</tbody>
</table>

Intranasal (IN) administration of IR Oxycodone HCl produced a maximum oxycodone plasma concentration \( C_{\text{max}} = 60.9 \) ng/mL that was significantly greater than that produced following either Xtampza ER IN or intact oral Xtampza ER. \( C_{\text{max}} \) following IR Oxycodone HCl was achieved sooner (median \( T_{\text{max}} \) of 2.58 hours) than the \( C_{\text{max}} \) following treatment with Xtampza ER administered IN or orally (median \( T_{\text{max}} \) of 5.08 hours). Total oxycodone exposure over the first 3 hours post-dosing, expressed in terms of \( \text{AUC}_{0-3\text{hrs}} \) was significantly higher following IR Oxycodone HCl IN (141 hr·ng/mL) compared to Xtampza ER either IN or orally administered (41.4 and 25.0 hr·ng/mL, respectively).

Oral Xtampza ER resulted in a higher oxycodone \( C_{\text{max}} \) but similar total oxycodone exposure compared to intranasally administered Xtampza ER.

**Results – Pharmacodynamic**

The Pharmacodynamic Population included subjects who completed all four Treatment Periods with at least one PD assessment in each Treatment Period.

The focus of this review will be on \( E_{\text{max}} \) of the primary measure of Drug Liking VAS and the secondary measures of High VAS and Take Drug Again VAS. Due to the fact that the Sponsor is proposing to include language under Section 9.2 of the label concerning the ARCI/MBG scale, this measure of euphoria is also examined.

This review will use the statistical review of Study CP-OXYDET-21 conducted by the CDER Office of Biostatistics (DARRTS, NDA 208-090, August 21, 2015, Author: Anna Sun, Ph.D.). This report provides descriptive statistics, statistical analysis, and percentage reduction for \( E_{\text{max}} \) from the Drug Liking VAS, High VAS, Take Drug Again VAS, and the ARCI/MBG scale.

**Results – Drug Liking VAS – Primary Measure**

The primary measure of the study was Drug Liking VAS. For assessing Drug Liking, subjects were asked the question “Do you like the effect that you are feeling now?” The question was scored using a
0-100 mm bipolar VAS anchored on the left with “strong disliking” (score of 0); “neither like nor dislike” (score of 50) in the middle; and anchored on the right with “strong liking” (score of 100).

Descriptive statistics and statistical analysis of \( E_{\text{max}} \) for Drug Liking VAS are shown in Tables 19 and 20, respectively.

Table 19. Descriptive Statistics for \( E_{\text{max}} \) of Drug Liking VAS, High VAS, Take Drug Again VAS, and the ARCI/MBG Scale in PD Population (N=36) (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Subjective Measure</th>
<th>Treatment</th>
<th>Mean ( E_{\text{max}} )</th>
<th>Standard Deviation</th>
<th>Minimum</th>
<th>First Quartile</th>
<th>Median</th>
<th>Third Quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-100 mm Bipolar Drug Liking VAS</td>
<td>A: Xtampza ER 40 mg IN</td>
<td>61.81</td>
<td>15.64</td>
<td>16.00</td>
<td>50.00</td>
<td>59.50</td>
<td>72.50</td>
<td>94.00</td>
</tr>
<tr>
<td></td>
<td>B: Xtampza ER 40 mg PO</td>
<td>67.75</td>
<td>13.84</td>
<td>46.00</td>
<td>58.00</td>
<td>67.50</td>
<td>78.00</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>C: IR Oxycodone 40 mg IN</td>
<td>82.72</td>
<td>10.95</td>
<td>60.00</td>
<td>74.00</td>
<td>84.00</td>
<td>90.00</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>D: Placebo</td>
<td>54.50</td>
<td>11.77</td>
<td>28.00</td>
<td>50.00</td>
<td>51.00</td>
<td>53.00</td>
<td>93.00</td>
</tr>
<tr>
<td>0-100 mm Unipolar Drug High VAS</td>
<td>A: Xtampza ER 40 mg IN</td>
<td>23.81</td>
<td>24.63</td>
<td>0.00</td>
<td>2.50</td>
<td>22.00</td>
<td>38.00</td>
<td>92.00</td>
</tr>
<tr>
<td></td>
<td>B: Xtampza ER 40 mg PO</td>
<td>34.83</td>
<td>25.12</td>
<td>0.00</td>
<td>13.00</td>
<td>29.50</td>
<td>51.50</td>
<td>97.00</td>
</tr>
<tr>
<td></td>
<td>C: IR Oxycodone 40 mg IN</td>
<td>69.50</td>
<td>25.18</td>
<td>12.00</td>
<td>53.00</td>
<td>71.50</td>
<td>88.00</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>D: Placebo</td>
<td>14.64</td>
<td>25.30</td>
<td>0.00</td>
<td>1.00</td>
<td>1.50</td>
<td>14.50</td>
<td>88.00</td>
</tr>
<tr>
<td>0-100 mm Bipolar Take Drug Again VAS</td>
<td>A: Xtampza ER 40 mg IN</td>
<td>47.67</td>
<td>27.84</td>
<td>0.00</td>
<td>30.00</td>
<td>50.00</td>
<td>60.00</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>B: Xtampza ER 40 mg PO</td>
<td>58.61</td>
<td>22.54</td>
<td>2.00</td>
<td>50.00</td>
<td>59.00</td>
<td>71.50</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>C: IR Oxycodone 40 mg IN</td>
<td>71.36</td>
<td>23.49</td>
<td>18.00</td>
<td>56.50</td>
<td>78.50</td>
<td>87.50</td>
<td>100.00</td>
</tr>
<tr>
<td></td>
<td>D: Placebo</td>
<td>45.92</td>
<td>17.50</td>
<td>0.00</td>
<td>50.00</td>
<td>50.00</td>
<td>50.00</td>
<td>97.00</td>
</tr>
<tr>
<td>16 Point ARCI/MBG Scale</td>
<td>A: Xtampza ER 40 mg IN</td>
<td>1.56</td>
<td>2.61</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>2.00</td>
<td>9.00</td>
</tr>
<tr>
<td></td>
<td>B: Xtampza ER 40 mg PO</td>
<td>3.17</td>
<td>3.98</td>
<td>0.00</td>
<td>0.00</td>
<td>1.50</td>
<td>4.50</td>
<td>14.00</td>
</tr>
<tr>
<td></td>
<td>C: IR Oxycodone 40 mg IN</td>
<td>5.94</td>
<td>4.82</td>
<td>0.00</td>
<td>3.00</td>
<td>4.00</td>
<td>9.00</td>
<td>16.00</td>
</tr>
<tr>
<td></td>
<td>D: Placebo</td>
<td>1.08</td>
<td>2.78</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1.00</td>
<td>15.00</td>
</tr>
</tbody>
</table>

The active comparator, IR Oxycodone 40 mg IN, produced an \( E_{\text{max}} \) of Drug Liking (LS mean of 82.57 mm) that was significantly (p<0.0001) above that produced by placebo IN (LS mean of 54.63 mm), thereby validating the study with respect to Drug Liking VAS.

Intranasal administration of 40 mg IR Oxycodone produced an \( E_{\text{max}} \) of drug liking (LS mean of 82.57 mm) that was significantly higher (p<0.0001) than that produced by either intranasal 40 mg Xtampza ER (LS mean of 61.88 mm) or by oral 40 mg Xtampza ER (LS mean of 67.87 mm). The \( E_{\text{max}} \) of drug liking following oral intact 40 mg Xtampza ER was just barely significantly higher (p=0.0343) than that produced by intranasal 40 mg Xtampza ER. These data suggests a potential abuse deterrent effect to intranasal abuse of Xtampza ER.

The median times to reach \( E_{\text{max}} \) (namely, \( T_{E\text{max}} \)) were 0.50 hours, 1.50 hours, and 3.00 hours for intranasal 40 mg IR Oxycodone, intranasal 40 mg Xtampza ER, and oral 40 mg Xtampza ER respectively. Statistical analysis of LS mean differences showed that the \( T_{E\text{max}} \) following intranasal 40 mg IR Oxycodone was significantly less than the \( T_{E\text{max}} \) following either intranasal or oral Xtampza ER.
Table 20. Statistical Analysis of the Mean Differences in $E_{\text{max}}$ for Drug Liking VAS in PD Population (N=36) (Source: CDER Office of Biostatistics)

| Treatments                                      | LS Mean | Standard Error | Pr > |t|  | Lower Confidence Limit | Upper Confidence Limit |
|-------------------------------------------------|---------|----------------|-------|---|------------------------|------------------------|
| A: Crushed Xtampza ER 40 mg IN                  | 61.8790 | 2.1985         | <.0001|  | 57.5183                | 66.2397                |
| B: Intact Xtampza ER 40 mg Dosed PO             | 67.8682 | 2.1985         | <.0001|  | 63.5075                | 72.2289                |
| C: Crushed IR Oxycodone HCl 40 mg IN            | 82.5730 | 2.1985         | <.0001|  | 78.2123                | 86.9336                |
| D: Placebo                                      | 54.6271 | 2.1985         | <.0001|  | 50.2664                | 58.9878                |

| LS Mean Treatment Differences                    |         |                |       |   |                        |                        |
| Treatment A vs. Treatment C                      | -20.6940| 2.7909         | <.0001|  | -26.2296               | -15.1583               |
| Treatment A vs. Treatment B                      | -5.9892 | 2.7919         | 0.0343|  | -11.5270               | -0.4514                |
| Treatment B vs. Treatment C                      | -14.7048| 2.7919         | <.0001|  | -20.2425               | -9.1670                |

Table 21 below provides the percentage of subjects displaying reductions in $E_{\text{max}}$ of drug liking following intranasal treatment with 40 mg Xtampza ER compared to intranasal 40 mg IR Oxycodone HCl. As noted in the table, 33 out of 36 subjects (91.67%) had some reduction in $E_{\text{max}}$ of drug liking following intranasal 40 mg Xtampza ER compared to intranasal 40 mg IR Oxycodone HCl. Twenty-eight subjects (78%) and 21 subjects (58%) had at least 30% and 50% reductions in $E_{\text{max}}$ of drug liking following intranasal 40 mg Xtampza ER compared to intranasal IR Oxycodone HCl.

Table 21. Percentage Reduction of $E_{\text{max}}$ of Drug Liking VAS, Treatment A (Xtampza ER IN) Vs Treatment C (IR Oxycodone HCl IN) (PD Population, N=36). (Source: CDER Office of Biostatistics)

<table>
<thead>
<tr>
<th>Percentage of Reduction (%)</th>
<th>Frequency</th>
<th>Percentage of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0</td>
<td>33</td>
<td>91.67</td>
</tr>
<tr>
<td>≥10</td>
<td>31</td>
<td>86.11</td>
</tr>
<tr>
<td>≥20</td>
<td>30</td>
<td>83.33</td>
</tr>
<tr>
<td>≥30</td>
<td>28</td>
<td>77.78</td>
</tr>
<tr>
<td>≥40</td>
<td>24</td>
<td>66.67</td>
</tr>
<tr>
<td>≥50</td>
<td>21</td>
<td>58.33</td>
</tr>
<tr>
<td>≥60</td>
<td>15</td>
<td>41.67</td>
</tr>
<tr>
<td>≥70</td>
<td>15</td>
<td>41.67</td>
</tr>
<tr>
<td>≥80</td>
<td>14</td>
<td>38.89</td>
</tr>
<tr>
<td>≥90</td>
<td>12</td>
<td>33.33</td>
</tr>
<tr>
<td>≥100</td>
<td>10</td>
<td>27.78</td>
</tr>
</tbody>
</table>
Results – High VAS

For assessing the secondary measure of High VAS, subjects were asked the question “How high are you now?” Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by “none” (score of 0) and on the right by “extremely” (score of 100).

Descriptive statistics for $E_{max}$ of High VAS is shown in Table 19 while statistical analysis of least square mean differences among treatments is provided in Table 22.

The active comparator, IR Oxycodone HCl 40 mg IN, produced an $E_{max}$ of high VAS (LS mean of 69.05 mm) that was significantly (p<0.0001) above that produced by placebo IN (LS mean of 14.59 mm), thereby validating the study with respect to Liking VAS.

The results of High VAS paralleled the results observed for Drug Liking VAS. Intranasal administration of 40 mg IR Oxycodone HCl produced an $E_{max}$ of high (LS mean of 69.05) that was significantly higher (p<0.001) than that produced by either intranasal 40 mg Xtampza ER (LS mean of 23.78 mm) or by oral 40 mg Xtampza ER (LS mean of 34.70 mm).

The $E_{max}$ of high following 40 mg Xtampza ER IN was significantly lower (p=0.047) than that for 40 mg Xtampza ER oral but similar (p>0.05) to that produced by placebo. Oral Xtampza ER 40 mg did produce a level of high significantly (p<0.05) above that of placebo.

Overall, the data derived using the High VAS suggests a potential deterrent effect of Xtampza ER to intranasal abuse.

Table 22. Statistical Analysis of the LS Mean Differences in $E_{max}$ for High VAS in PD Population (N=36) (Source: CDER Office of Biostatistics)

| 0-100 Point Unipolar High VAS Emax (mm) | LS Mean Emax | Standard Error | Pr > |t| | Lower Confidence Limit | Upper Confidence Limit |
|----------------------------------------|---------------|----------------|-------|----------------|------------------------|------------------------|
| Treatments                             |               |                |       |               |                        |                        |
| A: Crushed Xtampza ER 40 mg IN         | 23.7769       | 4.1649         | <.0001| 15.5159        | 32.0379                |
| B: Xtampza ER 40 mg Dosed PO           | 34.6976       | 4.1649         | <.0001| 26.4366        | 42.9587                |
| C: Crushed IR Oxycodone HCl 40 mg IN   | 69.0535       | 4.1649         | <.0001| 60.7925        | 77.3146                |
| D: Placebo                             | 14.5879       | 4.1649         | 0.0007| 6.3269         | 22.8489                |

LS Mean Treatment Differences

| Treatment A vs. Treatment C            | -45.2767      | 5.4283         | <.0001| -56.0437       | -34.5096               |
| Treatment A vs. Treatment B           | -10.9208      | 5.4304         | 0.0470| -21.6920       | -0.1495                |
| Treatment B vs. Treatment C           | -34.3559      | 5.4304         | <.0001| -45.1271       | -23.5847               |
Results – Take Drug Again VAS

The Take Drug Again VAS assessment involved asking subjects the question, “Would you want to take the drug you just received again, if given the opportunity?” The question was scored using a 0-100 mm bipolar VAS anchored on the left with “definitely would not” (score of 0); “do not care” (score of 50) in the middle; and anchored on the right with “definitely would” (score of 100).

Descriptive statistics for $E_{\text{max}}$ of Take Drug Again VAS is shown in Table 19 while statistical analysis of least square mean differences among treatments is provided in Table 23.

The active comparator, IR Oxycodone HCl 40 mg IN, produced an $E_{\text{max}}$ of Take Drug Again VAS (LS mean of 71.25 mm) that was significantly (p<0.0001) above that produced by placebo IN (LS mean of 46.24 mm), thereby validating the study with respect to Take Drug Again VAS.

Subjects expressed a willingness, if given the opportunity, to again insufflate 40 mg IR Oxycodone HCl (LS mean of 71.25) but an ambivalence to further insufflate either 40 mg Xtampza ER (LS mean of 47.78 mm) or placebo (LS mean of 46.24 mm). Subjects expressed some willingness (significantly, p<0.05, above placebo) to take again 40 mg Xtampza ER oral (LS mean of 59.00 mm), but this was significantly less (p = 0.014) than that for 40 mg IR Oxycodone IN. This observation provides further support that Xtampza ER may provide resistance to abuse by insufflation.

Overall, data obtained using the Take Drug Again VAS supports a potential deterrent effect of Xtampza ER to intranasal abuse.

Table 23. Statistical Analysis of the LS Mean Differences in $E_{\text{max}}$ for Take Drug Again VAS in PD Population (N=36) (Source: CDER Office of Biostatistics)

| 0-100 Point Take Drug Again VAS $E_{\text{max}}$ (mm) | LS Mean $E_{\text{max}}$ | Standard Error | Pr > |t| | Lower Confidence Limit | Upper Confidence Limit |
|-----------------------------------------------------|--------------------------|----------------|------|-------------|------------------------|------------------------|
| **Treatments**                                      |                          |                |      |             |                        |                        |
| A: Crushed Oxycodone DETERx 40 mg IN               | 47.7729                  | 3.8814         | <.0001| 40.0742     | 55.4715                |
| B: Intact Oxycodone DETERx 40 mg Dosed PO          | 58.9832                  | 3.8814         | <.0001| 51.2846     | 66.6819                |
| C: Crushed IR Oxycodone HCl 40 mg IN               | 71.2489                  | 3.8814         | <.0001| 63.5503     | 78.9476                |
| D: Placebo                                         | 46.2429                  | 3.8814         | <.0001| 38.5442     | 53.9415                |
| **LS Mean Treatment Differences**                  |                          |                |      |             |                        |                        |
| Treatment A vs. Treatment C                         | -23.4760                 | 4.8979         | <.0001| -33.1911    | -13.7610               |
| Treatment A vs. Treatment B                         | -11.2104                 | 4.8998         | 0.0242| -20.9291    | -1.4916                |
| Treatment B vs. Treatment C                         | -12.2657                 | 4.8998         | 0.0139| -21.9845    | -2.5469                |

Reference ID: 3817310
Results – ARCI/MBG Scale

The ARCI/MBG subscale is used to assess euphoria and positive mood, with each item scored on a 2-point scale (0-1), where 0 = false, 1 = true. The total score is calculated by adding the individual scores, with a possible total score of 16 for the MBG subscale (questions 1-16).

Descriptive statistics for $E_{\text{max}}$ of ARCI/MBG scale is shown in Table 19 while statistical analysis of least square mean differences among treatments is provided in Table 24.

The active comparator, IR Oxycodone HCl 40 mg IN, produced an $E_{\text{max}}$ on the ARCI/MBG scale (LS mean of 5.92 mm) that was significantly (p<0.0001) above that produced by placebo IN (LS mean of 1.11), thereby validating the study with respect to the ARCI/MBG scale.

Treatment with IR Oxycodone HCl 40 mg IN produced an $E_{\text{max}}$ on the ARCI/MBG scale (LS mean of 5.02) that was significantly higher (p≤0.001) than treatment with either 40 mg Xtampza ER IN (LS mean of 1.58) or 40 mg Xtampza ER oral (LS mean of 3.16) thereby indicating a greater degree of euphoria produced by the positive comparator compared to intranasal or oral Xtampza ER.

As reflected using the ARCI/MBG scale, there was no significant difference (p=0.564) in the degree of euphoria produced by intranasal and oral 40 mg Xtampza ER. When compared to placebo, oral 40 mg Xtampza ER (p<0.05), but not 40 mg Xtampza ER IN (p>0.05) produced significant euphoria.

Overall the assessment using the ARCI/MBG scale supports a potential deterrent effect of Xtampza ER to intranasal abuse.

Table 24. Statistical Analysis of the LS Mean Difference in $E_{\text{max}}$ for ARCI/MBG Scale in PD Population (N=36) (CDER Office of Biostatistics)

| ARCI/MBG Scale 16-Points | LS Mean $E_{\text{max}}$ | Standard Error | Pr > |t| | Lower Confidence Limit | Upper Confidence Limit |
|---------------------------|--------------------------|----------------|---------|--------------------------|---------------------------|
| A: Crushed Xtampza ER 40 mg IN | 1.5768 | 0.6189 | 0.0123 | 0.3491 | 2.8045 |
| B: Intact Xtampza ER 40 mg PO | 3.1570 | 0.6189 | <.0001 | 1.9293 | 4.3846 |
| C: Crushed IR Oxycodone HCl 40 mg IN | 5.9222 | 0.6189 | <.0001 | 4.6945 | 7.1499 |
| D: Placebo | 1.1052 | 0.6189 | 0.0771 | -0.1225 | 2.3329 |

| LS Mean Treatment Differences | | | | | |
| Treatment A vs. Treatment C | -4.3454 | 0.8185 | <.0001 | -5.9690 | -2.7219 |
| Treatment A vs. Treatment B | -1.5802 | 0.8189 | 0.0564 | -3.2044 | 0.04402 |
| Treatment B vs. Treatment C | -2.7653 | 0.8189 | 0.0010 | -4.3895 | -1.1410 |
Nasal Effects Subject Rated Assessment

Subject rated nasal assessments were conducted during the Treatment Phase in the safety population which consisted of 37 subjects receiving Xtampza ER IN, 38 subjects receiving IR Oxycodone HCl 40 mg IN, and 37 subjects receiving placebo. Nasal effects assessments included an assessment of: 1) nasal irritation, 2) burning, 3) need to blow nose, 4) runny nose/nasal discharge, 5) facial pain/pressure, and 6) nasal congestion.

In general, each of the six categories of nasal effects, were more frequently reported by subjects intranasally (IN) administering Oxycodone DETERx than IR Oxycodone HCl. For all categories peak effects were reached within 15 minutes and thereafter dissipated over the next 2 to 4 hours. Note the following percentages of subjects reporting moderate or severe effects at 15 minutes post-dosing:

- Nasal irritation – 48.6% taking Xtampza ER IN vs 5.2% taking IR Oxycodone HCl IN
- Nasal burning - 56.7% taking Xtampza ER IN vs 7.7% taking IR Oxycodone HCl IN
- Facial pain pressure - 37.8% taking Xtampza ER IN vs 2.6% taking IR Oxycodone HCl IN
- Nasal congestion - 27.0% taking Xtampza ER IN vs 2.6% taking IR Oxycodone HCl IN
- Nasal discharge – 37.8% taking Xtampza ER IN vs 2.6% taking IR Oxycodone HCl IN
- Need to blow nose – 48.6% taking Xtampza ER IN vs 4% taking IR Oxycodone HCl IN

4.4 Evidence of abuse, misuse and diversion in clinical trials

Sponsor conducted an analysis of adverse events suggestive of potential drug abuse in pivotal Phase 3 study CP-OXYDET-08 entitled “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-Naïve Subjects with Moderate-to-Severe Chronic Low Back Pain.”

Study CP-OXYDET-08 was a randomized, double-blind, placebo-controlled study, in which opioid-naïve subjects were entered into an open-label Titration Phase with Oxycodone DETERx for up to 6 weeks followed by a 12-week Double-blind Maintenance Phase for which they received either a stable dose of Oxycodone DETERx or placebo. Overall, 740 subjects were enrolled and treated with at least one dose of study drug; these subjects were included in the Safety Population. Of the 740 subjects enrolled, 389 (52.6%) subjects completed the Titration Phase and were randomly assigned to the Oxycodone DETERx (n = 193) and placebo (n = 196) treatment groups. All 389 randomized subjects were included in the Randomized Safety Population

Adverse Events Associated With Abuse

During the titration phase (open label) of study CP-OXYDET-08 involving 740 subjects, “euphoric mood” as an adverse event was reported by 6 subjects with severity noted as “moderate” in one case and as “mild” in the remaining 5 cases. With post-adjudication, in two cases there was a definite relationship of the adverse event to Xtampza ER treatment, while in the remaining 4 cases there was a “probable” relationship. Case report forms were provided for the six cases.

- White Male, born 1955 - two episodes of euphoric feeling – “Moderate” – “Definitely” related to study treatment - Second resulting in study discontinuation. Relationship to study treatment was considered “definitely.”
• Black Male, born 1963 - Euphoria - “Mild – Probably related to study treatment - Subject covered - Permanently discontinued from study.
• Black, Male, born 1944 – Euphoria – “Mild” – “Probably related to study treatment - No action taken with study drug.
• White, Male, born 1991 – Euphoria – “Mild” – Probably related to study treatment – Permanently discontinued from study

During the double-blind, Maintenance Phase involving a total of 193 subjects receiving Xtampza ER, 1 subject reported “Euphoric Mood” and a second subjected reported “Feeling Abnormal.” Case report forms were provided.
• White, Female, born 1940 - Feeling Abnormal (“weird sensation”) – “Mild” – Unlikely related to study treatment – Alternative causality unknown - No action was taken with study drug

In the course of conducting study CP-OXYDET-08 there were no reports documenting purposeful use of study drug to get high, tampering of study drug, or attempts to take study drug by alternative routes of administration.

Cases of Misuse

There were 4 cases of probable misuse of Xtampza ER during to open-label Drug Titration phase of study CP-OXYDET-08.
• At titration visit 4, subject reported self-medicating due to inadequate pain relief, taking 8 additional Xtampza capsules of study drug. Subject was discontinued from study.
• Subject reportedly could not tolerate her pain level despite taking morning and evening prescribed dose of study drug and maximum amount of rescue drug, so subject took 4 extra 10 mg Xtampza capsules of study drug. Subject reeducated on taking study drug.
• Subject reported that he had taken 6 extra doses of Xtampza when he was in pain. Investigator considered this to be study drug diversion and therefore discontinued subject from the study.
• Subject took 1 extra dose (4 Xtampza capsules) due to pain. Subject was discontinued from study due to lack of efficacy.

There were 2 cases of probable misuse of treatments during the double blind Maintenance Phase of study CP-OXYDET-08.
• At scheduled visit, subject reported that she took 4 extra Xtampza capsules because of pain. Subject was counseled against taking extra doses of study drug.
• While in the placebo treatment group, subject took 6 additional doses (24 capsules) of study drug over a 20-hour period because he was in pain. Assessment showed no withdrawal. Subject was discontinued from study due to lack of efficacy.
Cases of Withdrawal

During the Titration Phase and Double-Blind Maintenance Phase of study CP-OXYDET-08 21 subjects and 14 subjects, respectively, reported adverse events categorized as withdrawal. Following an independent assessment (adjudication) of these 35 total cases, 16 cases contained information that when collectively evaluated lead to reclassification of these cases to “no withdrawal” post adjudication. Of the remaining 19 cases, 4 cases were withdrawal attributable to the prior opioid at the start of the Titration Phase, and 15 cases were withdrawal related or potentially related to Xtampza ER treatment.

No adverse events associated with drug overdose were identified in Study CP-OXYDET-08.

Cases Involving Diversion

Based on investigators’ assessments, there were 9 cases of diversion during the Titration Phase and 3 cases of diversion during the Double-Blind Maintenance Phase. Ten of the subjects were discontinued as a result of the diversion (confirmed or suspected). Subjects involved in the remaining 3 cases were discontinued for other reasons.

Post-adjudication assessment by an expert outside reviewer identified 19 cases divided into the following three groups:

- 7 Cases of Suspected Diversion – discrepancy in drug accounting, or the subject reported throwing away unused study drug.
- 7 Cases of Suspected Diversion – subjects’ urine drug screens tested negative for oxycodone even though they reported taking Xtampza ER during the Titration Phase.
- 5 Cases of Confirmed Diversion – theft of study drug was reported.

Events of Noncompliance – Results of Adjudication

Examination by an outside expert identified 57 cases of noncompliance of study drug administration during the duration (total of 18 weeks) of study CP-OXYDET-02. A breakdown of these cases is as follows:

- 51 Cases - less than 3 extra doses (8 or fewer capsules) taken.
- 2 Cases – 3 to 4 extra doses (12 to 16 capsules) were taken
- 4 Cases – 5 to 6 extra doses (20 to 24 capsules) were taken.

5. Regulatory issues and assessment

As a product containing oxycodone, Xtampza ER Capsules are in Schedule II of the federal Controlled Substances Act.

At this time, CSS has no comments regarding the proposed language from Sponsor regarding the label of Xtampza ER Capsule

Xtampza ER Capsules will be taken to an advisory committee.
6. **Other relevant information**

Xtampza ER Capsules have not been previously marketed in the United States or other countries.
Appendix

Below is the OPQ review of the in vitro abuse deterrent studies.

Abuse Deterrence Studies
Abusers attempt to obtain rapid exposure and onset of the active of a drug product that they abuse. Abuse deterrent products typically contain mechanisms to allow the normal release of the active to achieve its therapeutic effect while simultaneously deterring the abusers efforts to obtain rapid release of the active. The applicant conducted a full range of extensive tests to assess the abuse deterrence properties of the drug product DETERx 40 mg in reference to the comparators Roxicodone 30 mg and OxyContin OP 40 mg.

Because of the large volume of contents provided, only critical information relevant to the assessment of the test results are summarized below. Where the applicant already have a concise summary, the summary is excerpted and edited to more accurately reflect the provided data.

**Study # 1 – Physical Manipulation**
Since particle size reduction is a common first step abusers employ to increase the release rate of a product, the applicant tested different particle size reduction (PSR) approaches using commonly available household tools and how it affected the release of the API. Release is tested using a validated dissolution method using paddle instead of basket (for the drug product capsule) to accommodate the testing of powders. The 40 mg Oxycodone DETERx capsules were studied in comparison to the 40 mg OxyContin OP tablets.

A broad range of size reduction tools were considered, those selected for the study include rotating food chopper, blade based pill cutter, cheese grater, mortar and pestle, hammer, metal garlic press, pill crusher (with teeth), pepper mill, herb mill and coffee grinder. Because the drug product contains very small waxy beads (approximately 180-240 μm), particle size reduction with some of the tools was not possible due to apparent lack of contact. The applicant performed the particle size reduction for 2 minutes in general for procedures that are better controlled with a timed stop. The time of 2 minutes was selected based on the particle size reduction method optimization studies that found mortar and pestle to be the most effective tool (at a grinding speed of ~ 100 rpm and a grinding time of 2 minutes) to allow optimal oxycodone dissolution. However, for approaches such as grating, the process was to complete grating the test tablet.

Nine of the 11 tools applied to Oxycodone DETERx produced <10% change in the particle size of the beads. Those techniques that did reduce particle size of the Oxycodone DETERx Capsules did not result in dose dumping (fast and significant release) in vitro when subjected to dissolution. The most effective technique is grinding with a mortar and pestle. The sample ground with the mortar and pestle showed the most significant impact on oxycodone release rate compared to the control sample but without dose dumping.

Eight of the 11 tools applied to OxyContin OP impacted the integrity of the tablet, at a minimum producing deformation and in the worst cases reducing the tablet into small chunks or particles. Those PSR techniques that successfully reduced the OxyContin OP Tablets to small chunks or particles
increased the in vitro release rate of oxycodone considerably and, in some cases, resulted in dose dumping. The most effective technique is PSR with a fine grater.

The applicant stated that the coffee grinder did have productive PSR for OxyContin OP Tablets for three of the six tablets tested. And these three tablets showed a significant increase in dissolution at the early time points. Three tablets remained intact and had similar release profiles to the whole tablets (Control).

A separate study evaluated how pretreatment with heating or freezing affected particle size reduction of the DETERx beads. They tested three different particle size reduction techniques, grinding with mortar and pestle, grinding with a coffee grinder, and chopping with a food chopper. The subsequent sample particle size distributions and oxycodone dissolution were characterized. The applicant found that upon heating, the beads melt and then fused into a single mass as it cooled down, it then was not easy to be reduced to smaller particles. The subsequent dissolution was slower than without pre-treatment with heating. The largest change in particle size was from the coffee grinder freezing sample followed by the mortar and pestle control and the mortar and pestle freezing samples. All the other techniques had less than 5% change in particle size at D10, D50 and D90 when compared to the control without heating or freezing and PSR. However, the overall observed changes in the particle size distribution were relatively small (less than 20% change) and similar between PSR with the various pre-treatments and their respective controls. Therefore freezing practically does not enhance the PSR of oxycodone DETERx beads relative to PSR without pre-treatment. Since heating and freezing did not significantly affect the PSR of the study drug DETERx, they did not perform the same study for the comparator products. Generally a decrease in particle size correlated with an increase in release rate. Dissolution testing of the samples were tested up to 24 hours. The largest difference in dissolution occurred at early sampling times and it decreased as sampling time increased. Overall, the DETERx samples that had no heating or freezing treatments and ground with mortar and pestle showed faster dissolution than all other samples. Therefore the applicant selected mortar and pestle as the technique to continue with subsequent studies that involves PSR.

Evaluation: Noted. Under the study conditions, the Oxycodone DETERx was less prone to particle size reduction than the comparator product. This obviously is due to its dramatically smaller starting size of approximately 4 µm in contrast to a regular tablet and soft waxy composition. Note that the PSR was only performed for a duration of 2 minutes, which is the optimal PSR time for the mortar and pestle technique selected to grind the DETERx beads. Apparently the applicant used the 2 min PSR time with most other PSR methods to allow comparison. If the OxyContin OP comparator tablet is ground for longer than 2 minutes using a coffee grinder, more significant and consistent API release should be observed, perhaps much more significant than the samples obtained with the fine grater.

Study # 2 – Syringeability (Preparation for Intravenous Administration)

A. Syringing the water solution/suspension of the ground drug product

This study examined if and how much of the API of the Oxycodone DETERx (40 mg) and the comparator products OxyContin OP(40 mg) and Roxicodone (30 mg) can be prepared into injection under a standard set of operating conditions.

Individual OxyContin OP tablet was scraped along a fine grater to get a powder. The individual Roxicodone tablet and Oxycodone DETERx capsule were ground for 2 minutes with a ceramic mortar and pestle at approximately 100 rpm. The obtained powder from individual tablet/capsule samples was...
extracted with either 5 mL or 10 mL diluent by shaking for 5 seconds. Then attempts were made to draw the formed mixture into a syringe using 18, 22, 25 and 27 gauge needles respectively and then expelled for quantification. The API was quantified using an HPLC method that is also used in the drug product dissolution testing.

The applicant found that the amount of oxycodone recovered in the expelled volume was low (not more than 1.4%) for Oxycodone DETERx across the tested conditions of dilution volume and needle gauges. OxyContin OP and Roxicodone exhibited higher drug recoveries in the expelled volume when subjected to the same procedures and test conditions (maximum recoveries of 54% and 95%, respectively).

**Evaluation:** Noted. Under the study conditions, the Oxycodone DETERx exhibited much less efficiency when it was syringed. Because the applicant only shook the samples for 5 seconds and there is no heating the sample to facilitate the release of the API, it appears not clear how shaking the samples for a longer period of time, such as 3 minutes, and heating the sample would affect the API recovery from the oxycodone DETERx. Although it is reasonable for an abuser to shake for a couple of minutes and heat the sample to enhance dissolution, the hydrophobic waxy beads will not increase dissolution much, as indirectly illustrated in other extraction studies that involve both heating and continuous shaking.

**B. Syringing the water suspension of the intact drug product beads and molten beads**

The drug product formulation exists in tiny waxy beads. The applicant first evaluated if and how much of the formulation beads can be suspended in water and directly injected by an abuser. They transferred the drug product formulation content from the capsule into a syringe barrel, added 5 mL of water, mixed and then attempted to expel the suspension through 18, 22 and 27 gauge needles. The expelled beads are collected with a filter, dried, and weighed.

Only the 18 gauge needle was large enough to allow the passage of a measurable quantity of the formulation beads. The less concentrated preparation allowed more beads being expelled through the needle. For example, less than 0.6% formulation beads were recovered through the 18 gauge needle when the 40 mg strength was suspended in 5 mL of water, a very variable but up to 18.1% of beads were recovered when the 10 mg strength capsule (¼ in concentration compared to the 40 mg strength) was suspended in 5 mL of water.

In a separate report, the firm also reported that the average recovered beads was < 2% for intact beads and < 14% for crushed beads when suspended in 5 mL of water. The amount of beads passed through the 18 gauge needle is also very variable, with the largest variability observed with the 10 mL volume and crushed beads. The individual samples ranged from 1.1 mg (0.3%) solid recovered to 228.1 mg (54.2%). Meanwhile, the amount of active drug obtained in the expelled volume was low, with an average drug recovery of 0.6% for the 5 mL volume and 1.4% for the 10 mL volume. This obvious is because the hydrophobic beads do not release the oxycodone quickly into the water used to prepare the samples.

Considering that the formulation can melt at relatively low temperature, the applicant then evaluated if the drug product beads can be molten and injected. The beads were found to melt at 75oC. Using 18, 22, 25 and 27 gauge needles, they found that it was only feasible to draw the molten formulation into the syringe with the largest 18 gauge needle, but after the shortest amount of time (10 seconds), the material
solidified and could not be expelled. The 10 seconds hold time was selected to simulate the time required by abusers to remove air bubbles from the syringe and ready themselves for injection.

**Evaluation:** Noted. The study results indicate that it is not an efficient way to abuse the drug product by injecting the suspended formulation beads, intact or crushed. Only less than 20% of the 10 mg strength could be injected with the largest 18 gauge needle. Even after the injection, the waxy beads can still limit the release rate of the oxycodone. Because of the fast congealing of the formulation, it is impractical to abuse the drug product by melting the formulation, syringe and injecting it.

*Study # 3 – Small Volume Extraction (for IV Injection) – Study 1 (Immediate Sample Preparation & Analysis)*

This study is similar to the syringeability study in that the applicant used 5 and 10 mL water to extract the ground test product (40 mg strengths) and comparator products (OxyContin OP 40 mg and Roxicodone 30 mg), except in this study they also included 2 mL volume, tested effect of pre-heating the ground products, extracting with boiling water and only used the 27 gauge needle.

All tested products were particle size reduced. The DETERx was ground using a mortar and pestle for 2 minutes. The OxyContin OP tablets were crushed with a pill crusher or a microplane grater. The Roxicodone was tapped into fine powder using a pestle.

When the powders were extracted with 2, 5, and 10 mL of water at room temperature and immediately prepared for analysis, as expected, the Roxicodone had the highest API recovery, on average, reaching 62 to 88.5% LC. The OxyContin OP recoveries ranged 4.2 – 10.4% LC. While the DETERx had the least recoveries ranging 0.1 – 0.4%. With the increase of extraction volume, the recovery increased for all tested products.

When extracted with boiling water, on average, the Roxicodone had API recoveries reaching 78.8 – 94.8% LC. The OxyContin OP recoveries ranged 8.5 – 20.9% LC. While the DETERx had the least recoveries of 1.2 – 4.2%. With the increase of extraction volume, the recovery increased for all tested products. Apparently, with boiling water the extraction became significantly higher for all products although the DETERx and OxyContin recoveries were still much lower than that of the non-abuse deterrent Roxicodone.

When the DETERx and OxyContin powders ground to relatively coarse and fine particle sizes were first treated with heat (~ 180oC, duration is not stated) and then extracted with 5 mL of boiling water, the OxyContin recoveries, on average, were 45.6% LC for the coarser particles (prepared with tablet crusher) and 67.8% for the finer particles (prepared with the microplane grater). There is a significant increase compared to the recovery of 17.1% LC with 5 mL of boiling water but no pretreatment with heat. The significant difference is said due to the destruction of the PEO’s gelling property in OxyContin OP. In contrast, the treated DETERx powder had a recovery of 1.7% LC API.

For each extraction condition, the applicant also studied how increasing the strength among 10 mg, 20 mg, and 40 mg for DETERx would affect the API recovery. In general, product strength had no meaningful effect on the API recoveries in mass mainly because of the overall low recoveries. The % recoveries ranged between 0.1 – 7.9% LC for all studies conditions.
Evaluation: Noted. Under the study conditions, the Oxycodone DETERx exhibited much lower recoveries compared to the comparators. The lower recoveries were partially due to the abuse deterrent mechanism and partially due to the difference in the API used. The study drug API is oxycodone base that potentially has formed a salt with the excipient myristic acid, the oxycodone myristate is expected to have much lower water solubility than its hydrochloride salt used as API in the two comparator products. The provided data indicate that Oxycodone DETERx is less abuse prone compared to the comparator products.

Study # 4 – Small Volume Extraction (for IV Injection) – Study 2 (Delayed Sample Preparation & Analysis)
This study was expanded from the prior small volume extraction study using 5 and 10 mL of water as the solvent. It tested extraction time ranging from 0.5 to 30 minutes or until achieving > 80% LC recovery; it also tested pretreatment using a microwave and extraction sample viscosity.

All tested products were particle size reduced. The DETERx was ground using a mortar and pestle for 2 minutes at about 100 rpm. The OxyContin OP tablets were grated with a microplane grater. The Roxicodone was tapped into fine powder using a pestle.

For room temperature extraction, the crushed powder was placed into a scintillation vial and added the specified volume of water (5 mL or 10 mL). For 90 – 95oC extraction, the sample powder were microwaved for 8 minutes on full power using a 1200 watts microwave after it was stabilized via heating a placebo sample. The treated sample were then transferred into a scintillation vial and the specified volume of water heated to 90 – 95°C was added. The vial was placed into a water bath at 90 – 95°C. All vials were swirled intermittently manually for specified durations and sampled at defined time points, the hot samples were allowed to cool first, for quantification using a validated HPLC method. The 0.5 minute and 30 minute samples were also measured for viscosity.

Extraction with Water at Room Temperature
The DETERx microspheres had low oxycodone recoveries in 5 mL at room temperature. The highest recovery was 2.0% LC (0.8 mg) obtained from the crushed microspheres at 30 minutes. Crushing showed a slight increase in recoveries across all time points. The viscosity measurements of all samples were similar to that of water (~1.00 cP @ 20°C).

OxyContin showed substantial differences between intact and crushed product in 5 mL. Intact OxyContin demonstrated slow steady oxycodone extraction, reaching its peak extraction of 9.9% LC (4.0 mg) at the 30 minute time point. Intact OxyContin had viscosity measurements similar to that of water (~1.00 cP @ 20°C).

Crushed OxyContin showed an increase in oxycodone recovery ranging from 17.4 to 28.5% LC in 5 mL. Crushing also produced inconsistent results due to the gelling of the product making filtration difficult, yielding variable and low volume recovery. The crushed product’s variable recovery results show correlation to higher viscosity values, 2.85 cP at 0.5 minutes and increasing to 435 cP by the 30 minute time point.

Roxicodone tablets released readily in 5 mL of water at room temperature. Intact tablets reached complete oxycodone extraction within 15 minutes in water. Crushed tablets reached complete
oxycodone extraction at the 30 second time point. The viscosity measurements of all samples were similar to that of water (~1.00 cP @ 20°C).

When extracted with 10 mL water, the DETERx beads generally showed a small increase in recoveries for each studied time point in comparison to using 5 mL water. The increase is more pronounced for the crushed DETERx samples.

Similarly, the intact OxyContin tablet showed small increase in recoveries when extracted with 10 mL water. Significant increases were observed in the recoveries and decreases in viscosities of the extraction from the crushed OxyContin tablet powder, again, the results are variable.

Increasing extraction volume to 10 mL did not have any apparent impact to the recoveries from the Roxicodone tablets compared to using 5 mL water as the recoveries were nearly complete already.

**Extraction with Water at 90 – 95°C**

Oxycodone DETERx microspheres demonstrated low amounts of oxycodone extraction in 5 mL at 90-95°C. The highest extraction occurred with crushed and microwaved microspheres at 15 minutes of exposure, extracting 7.5% LC (3.0 mg). Intact and crushed microspheres showed similarity in extraction across all time points. Microwaving demonstrated a slight increase in extraction compared to intact microspheres with crushing alone. The viscosity measurements of all samples were similar to that of water (~1.00 cP @ 20°C).

Intact OxyContin extracted oxycodone over time, reaching its peak extraction of 48.8% LC (19.5 mg) at the 30 minute time point. Intact OxyContin had viscosity measurements similar to that of water (~1.00 cP @ 20°C) Crushed OxyContin demonstrated an initial increase in oxycodone extraction at the early time points of 0.5 minutes (21.3% LC) and 2 minutes (36.6% LC). The trend was weakened at the remaining time points due to the gelling of the product, which appeared to be enhanced due to exposure to elevated water temperatures. The gelling of the product made filtration difficult, yielding low volume recovery. The crushed product had variable recovery results that correlated with higher viscosity values, beginning with 204.3 cP at 0.5 minutes and increasing to 479 cP at 30 minutes.

Crushed and microwaved OxyContin demonstrated high oxycodone extraction and reached complete extraction at 15 minutes. This pretreatment method yielded 60.7% recovery (24.3 mg) at 0.5 minutes and reached completion at 15 minutes with 82.9% recovery (33.2 mg). Crushed and microwaved OxyContin had viscosity measurements similar to that of water (~1.00 cP @20°C). The low viscosity confirms that microwaving the crushed OxyContin increases extraction in water by destroying the gelling properties of the tablet excipient (polyethylene oxide).

Roxicodone tablets released oxycodone readily in 5 mL of water at 90-95°. Both intact and crushed tablets reached complete oxycodone extraction at the 30 second time point, at 88.3% and 88.6% respectively. The viscosity measurements of all samples were similar to that of water (~1.00 cP @ 20°C).

The figure reproduced below visually compares the effect of microwaving on all three tested products when extracted with 5 mL water at 90 – 95°C.
When extracted with 10 mL water, the DETERx beads generally showed a small increase in recoveries for each studied time point in comparison to using 5 mL water. The increase is more pronounced for the crushed DETERx samples. The highest extraction occurred with crushed microspheres at 30 minutes of exposure, extracting 11.2% LC (4.5 mg).

Similarly, the intact OxyContin tablet showed small increase in recoveries when extracted with 10 mL water. Some significant increases were observed in the recoveries and decreases in viscosities of the extraction from the crushed OxyContin tablet powder, but the results are very variable.

Increasing extraction volume to 10 mL did not have any apparent impact to the recoveries from the Roxicodone tablets compared to using 5 mL water as the recoveries were nearly complete already.

**Evaluation**: Noted. Under the study conditions, the Oxycodone DETERx exhibited much lower recoveries compared to the comparators. The lower recoveries were partially due to the abuse deterrent mechanism afforded by the product formulation composition. The provided data indicate that Oxycodone DETERx is less abuse prone compared to the comparator products.

*Study # 5 – Small Volume Extraction (for IV Injection) – Study 3 (with Microwave Pretreatment)*

The study drug DETERx 40 mg strength capsule beads were ground with a ceramic mortar and pestle for 2 minutes at approximately 100 rpm, microwaved for 8 minutes on full power in a 1200 watt microwave, cooled down, and then extracted with 5 mL of water heated to just started to boil. The comparator OxyContin 40 mg tablet was crushed with a fine grater and similarly prepared. The filtrate of both samples were analyzed to determine oxycodone recovery.

The oxycodone recovery from DETERx was an average (n = 3) of 3 mg (8% LC). The average from the OxyContin was 34 mg (84% LC).

**Evaluation**: Noted. Under the study conditions, the Oxycodone DETERx exhibited significantly more resistance to small volume near boiling point extraction post microwaving manipulation of the crushed product powder than the comparator OxyContin.
Study # 6 – Dissolution Following Soaking in Beverages
To characterize how different common beverages affect the release of the oxycodone, the product formulation beads from one 40 mg capsule were mixed with 30 mL each of different beverages, including Gatorade, Dasani (water), Cranberry Juice, Coca-Cola, Rockstar, 40% ethanol, vinegar, and allowed to soak for 10 minutes. The mixtures were then introduced into the dissolution apparatus and tested for oxycodone release over 24 hours.

As expected, the waxy beads tended to either float at the top of the aqueous beverages or stick to the walls of the container. The dissolution results reproduced below demonstrate that soaking the beads in a variety of beverages does not impact the in vitro release profile of Oxycodone DETERx Capsules. The beads retain their extended-release characteristics after soaking for 10 minutes in all beverages tested.

Evaluation: Noted. The study results indicate that by soaking the drug product formulation beads with various beverages for 10 minutes does not alter the release of the oxycodone. Due to the aqueous nature of the beverages and the hydrophobic nature of the waxy drug beads, the study was not designed to reveal what can occur with lipophilic solvents. However, that aspect has been covered in a separate extraction study using advanced solvents (Study # 7).

Study # 7 – Solvent Extraction (Using Relatively Large Volume and with Secondary Manipulation)
This study was said designed to challenge the formulation to the point of failure (in abuse deterrence) using more aggressive extraction conditions that simulate a range of methods used by both novice and experienced abusers. The study drug DETERx 40 mg and comparators OxyContin OP 40 mg and Roxicodone 30 mg were evaluated. The study includes four parts summarized below. Note that the Roxicodone was studied separately and only with continuous agitation. The reported results are integrated together in this review.
Part 1: Intact DETERx Capsule Contents (Microspheres), Roxicodone and OxyContin OP Tablets – Extraction with Ingestible Solvents at Room Temperature

Testing was conducted using 30 mL of each solvent at room temperature. The solvents include water, 3% sodium bicarbonate, Coca-Cola, olive oil, 40% ethanol, vinegar, and water at pH 4.9. The samples were either intermittently swirled (for 10 seconds prior to each sampling time point) or shaken continuously at 250 rpm.

Intact Roxicodone tablets exhibited ≥74% drug extraction in 1 hour in all solvents except olive oil. Very low extraction (<1%) over 24 hours was observed with olive oil.

Intact OxyContin OP tablets exhibited controlled extraction over time in most ingestible solvents, characterized by less than 30% release at the 2 hour time point for all solvents tested regardless of the method of agitation. Negligible extraction over 24 hours was observed with olive oil.

Extraction from intact DETERx microspheres was generally much lower than from intact Roxicodone and OxyContin OP tablets, except in olive oil and 40% ethanol where the respective extraction profiles were somewhat higher for intact DETERx than for intact Roxicodone and OxyContin OP. Agitation mostly did not have any apparent effect except it increased extraction with olive oil, although the overall extraction was still less than 10% by 24 hours.

Part 2: Crushed DETERx Capsule Contents (Microspheres), Roxicodone and OxyContin OP Tablets – Extraction with Ingestible Solvents at Room Temperature

This part is a repeat of Part 1 except it tested extraction from the particle size reduced (as described in previous studies) products.

Crushed Roxicodone tablets exhibited >75% drug extraction after 15 minutes in all ingestible solvents except olive oil. Very low extraction (<1%) over 24 hours was observed with olive oil.

Crushed OxyContin OP tablets exhibited near complete extraction (≥77%) after two hours in all ingestible solvents except bicarbonate and olive oil regardless of the method of agitation. The amount extracted plateaued after two hours near 50% for the 3% bicarbonate samples. Extraction was very low (< 3%) in olive oil.

Crushed DETERx microspheres exhibited controlled extraction over time in all ingestible solvents, characterized by less than 20% released at the 15 minute time point and less than 50% released at the 2 hour time point regardless of the method of agitation. The extraction profile over time for crushed DETERx microspheres was lower than for crushed Roxicodone and OxyContin OP tablets in all solvents except olive oil, where less than 10% was extracted from all products over 24 hours.

Continuous agitation was more effective than intermittent agitation in extracting API from crushed OxyContin OP tablets at early time points (<2 hours), whereas for crushed DETERx microspheres the extraction profile over time was similar for both methods of agitation. Under continuous agitation for 15 minutes, five of seven ingestible solvents extracted more than 70% of the API from crushed OxyContin OP tablets while for crushed DETERx microspheres, <10% of the API was extracted in all seven solvents tested. At 24 hours, extraction for crushed DETERx was still incomplete (<80%) for all but one solvent (40% ethanol).
Part 3: Crushed DETERx Capsule Contents (Microspheres), Roxicodone and OxyContin OP Tablets – Extraction with Ingestible Solvents at Elevated Temperatures (37°C and 60°C)
This part is a repeat of Part 2 except it tested extraction at elevated temperatures.

Crushed Roxicodone tablets exhibited >90% drug extraction after 15 minutes in all ingestible solvents except olive oil at both elevated temperatures (37°C and 60°C). Very low extraction (<3%) over 24 hours was observed with olive oil.

Crushed OxyContin OP tablets exhibited near complete extraction (≥79%) after one hour in all ingestible solvents except bicarbonate and olive oil at both elevated temperatures (37°C and 60°C).

At 37°C, crushed DETERx microspheres exhibited significantly lower extraction as compared with crushed Roxicodone and OxyContin OP tablets in six of the seven ingestible household solvents in the early time points (through 2 hours). For most solvents extraction was lower for crushed DETERx microspheres through 8 hours. Extraction in DI water and water adjusted to pH 4.9 was significantly lower for crushed DETERx microspheres than for crushed OxyContin OP tablets, and plateaued at ~20%. Although extraction in olive oil was higher for crushed DETERx microspheres than for crushed Roxicodone and OxyContin OP, it was incomplete over the time course studied (<50% released at 24 hours).

At 60°C, crushed DETERx microspheres exhibited significantly lower extraction when compared with crushed Roxicodone and OxyContin OP in six of the seven ingestible household solvents at the 15 minute time point. By 1 hour the amount extracted in Coca-Cola and vinegar was similar for DETERx and Roxicodone, and by 4 hours the amount extracted into 40% ethanol was similar. Extraction in bicarbonate plateaued for crushed Oxycodone DETERx at ~50%; extraction from crushed Roxicodone decreased over time at 60°C, possibly due to its limiting water solubility. OxyContin was slightly different. By 1 hour the extraction was similar for DETERx and OxyContin in three of the solvents (Coke, vinegar and 3% bicarbonate) and by 4 hours, a significant difference in the percent extracted was observed only in olive oil, DI water, and pH 4.9 water. Extraction in DI water and water adjusted to pH 4.9 was significantly lower for crushed DETERx microspheres than for crushed Roxicodone and OxyContin OP tablets (~5% for DETERx versus ~90% for Roxicodone and ~80% for OxyContin OP at 15 minutes), and plateaued at ~20%. Although extraction in olive oil was higher for crushed DETERx microspheres than crushed Roxicodone and OxyContin OP, it was incomplete over the time course studied (<50% released at 24 hours).

Part 4: Intact and Crushed DETERx Capsule Contents (Microspheres), Roxicodone and OxyContin OP Tablets – Extraction with Advanced Solvents at Room Temperature
Testing was conducted using 30 mL of each solvent at room temperature. The solvents include acetone, ethyl acetate, 1N HCl, 1 N NaOH, methanol, isopropanol and 95% ethanol. The samples were shaken continuously at 250 rpm. This first extraction is defined as the primary extraction. Since the solvents are not ingestible, a secondary extraction was conducted using 5 mL of water to further extract the active into a non-toxic abuseable form for injection or ingestion.

In primary extraction studies using intact microspheres or tablets, extraction in advanced organic solvents was generally higher when compared the intact Oxycodone DETERx microspheres with the intact OxyContin OP tablets at individual time points. When compared to the intact Roxicodone tablets,
the extraction from DETERx was higher at individual time points through 2 hours. By 2 hours, the amount extracted in 95% ethanol and methanol was comparable. Between the two aqueous solvents, the acidic solvent (1.0 N HCl) was much more effective in extracting drug from Roxicodone and OxyContin tablets than DETERx microspheres over time. The basic solvent (1.0 N NaOH) did not effectively extract drug from any product (<15% over 24 hours).

The two-step extraction procedure applied to intact Roxicodone and OxyContin OP tablets after primary extraction was effective, resulting in a significant recovery in water (56% to 70% for Roxicodone from the primary extractions when using 1.0N HCl, 95% ethanol, and methanol as the solvents; 47% for OxyContin OP from primary extraction using methanol as the solvent). Two-step extraction procedures applied to intact DETERx microspheres demonstrated relatively poor yields in water (< 5%) in all cases. Since the primary extraction in methanol was complete (> 95%), apparently the low yields in the secondary water extraction means that the active, probably exists as oxycodone myristate (in contrast to the oxycodone hydrochloride in Roxicodone and OxyContin OP), is not fully dissolved in water.

In primary extraction studies using crushed microspheres or tablets, crushed Oxycodone DETERx microspheres exhibited comparable extraction profiles in five of the seven advanced solvents tested when compared with crushed Roxicodone and OxyContin OP tablets. Extraction in 1.0 N HCl is significantly higher for crushed Roxicodone and OxyContin OP tablets when compared with crushed Oxycodone DETERx microspheres over the entire time course. Ethyl acetate was more effective in extracting API from crushed Oxycodone DETERx microspheres.

Two-step extraction procedures applied to crushed Roxicodone and OxyContin OP tablets were effective, resulting in significant recovery in water, ranging from 48% to 66% for Roxicodone and 37% to 84% for OxyContin OP, from five primary extraction solvents (isopropyl alcohol, acetone, 1.0 N HCl, 95% ethanol, and methanol). Two-step extraction procedures applied to crushed DETERx demonstrated relatively poor yields in water (<5%) in all cases, presumably due to the water solubility limitation of the API (that probably exists as oxycodone myristate).

Based on the results above, the applicant concluded that DETERx microspheres were generally more resistant to extraction in ingestible solvents across a range of solvents and experimental conditions when compared to Roxicodone and OxyContin OP tablets. Additionally, 2-step extractions (primary extraction into an advanced solvent and secondary extraction into water) were more effective in isolating oxycodone in an aqueous, abuseable solution when applied to Roxicodone and OxyContin OP tablets than when applied to Oxycodone DETERx microspheres.

**Evaluation**: Noted. The results provided support the summaries and conclusion the applicant made. Note that the secondary extractions were not completed as ordinary liquid-liquid extraction typically seen in chemical synthesis. The purpose here is to show relative behavior between the study drug DETERx and the comparators, and it has been achieved.

**Study # 8 – Simulated Smoking (Vaporization)**

In this study, the firm heated the study drug particle size reduced DETERx 40 mg strength formulation beads, OxyContin OP 40 mg tablets, and Roxicodone 30 mg tablets and collected the fumes generated. The collected fumes were cooled down and recovered, the residual samples were also recovered and analyzed.
The heating of the powder samples took place at 250°C with length of run at 1, 3, 5, 10 and 20 minutes to evaluate typical heating duration (1 – 5 minutes) and extended duration (10 and 20 minutes). The rationale of focusing on 250°C is based on literature showing that intermittent heating with a lighter produces this temperature. It was also conducted at 200 and 300°C respectively for 3 minutes to evaluate effect of different temperatures, thereby covering the real world scenario of inaccurate heating.

Results from testing the three products showed that at the baseline condition (250°C and heated for up to 5 minutes), the percent of oxycodone (relative to the claimed product strength) recovered from DETERx as vapor is similar to OxyContin. The average percent recovered from Roxicodone was higher than DETERx for the 1 and 3 minute time points. All products released less than 34% (on average) at the baseline condition. Oxycodone DETERx released higher quantities of inactive (excipient) vapor than both reference products; this was apparent by the higher mass loss from DETERx samples as well as the visual observation of vapor emission from the sample.

When subjected to heating over extended periods of time (10 and 20 minutes), Oxycodone DETERx showed a higher cumulative yield of oxycodone in the vapor phase than the reference products. Drug was not fully recovered in any of the products, with less than 60% average recovery in the vapor phase in all cases.

The effect of temperature (simulating inconsistent heating) study results showed that very little (≤ 9.0% LC) drug were recovered as fumes from all products, indicating 200°C as ineffective in volatilizing the oxycodone for any of the tested products. At 300°C, the average percent of drug recovered in the vapor was higher for DETERx than for OxyContin, but the difference between DETERx and Roxicodone were said not statistically significant due to large analytical variations. The release of active in the vapor was associated with a substantial vaporization of inactive components for the DETERx product; the mass of inactive released was much greater than for either of the reference products (~6-7 times as much inactive released into the vapor). Analysis of the pan residue showed that heating at 300°C for 3 minutes is sufficient to release or degrade most of the oxycodone in all 3 products (the mean recovery in the solid was ~13% or less).

**Evaluation**: Noted. The study results indicate that the study drug and the comparators behave relatively similarly when heated. The fume generated from the DETERx beads also contain a significant portion of inactive ingredients. Much of which is said to be myristic acid that is reported by its MSDS as a respiratory irritant. The firm did not find any published study to support this although they think it might help deter the abuse through smoking. Overall, smoking is not a preferred method to abuse oxycodone solid oral dosage form products, and the study drug DETERx capsule behave relatively similarly to the comparator products.

**Study # 9 – Independent Lab Verification**

In the Type B Pre-NDA meeting conducted on April 16, 2014, the Agency conveyed to the firm that “In vitro (abuse deterrent) studies should be done by an outside, independent laboratory”. However, most of the category 1 in vitro abuse deterrent studies were completed or already on-going in house. Therefore the firm had an independent outside laboratory to conduct and completed a subset of the studies regarding the effect of physical manipulation as a verification to their internal studies. The verification study results are summarized and evaluated below.
The study conducted by the outside laboratory include testing of three separate particle size reduction techniques on the study drug DETERx capsules and comparator OxyContin tablets. The DETERx capsules were ground with ceramic mortar and pestle, coffee grinder and food chopper. The OxyContin tablets were ground with fine grater, food chopper and modified tablet crusher. The powder samples formed via grinding or crushing were then tested for dissolution.

A. OxyContin Tablets
The percentage recovery between the two labs differ by less than two percent for each PSR technique.

All three techniques used for each product were effective in significantly increasing the dissolution rate of the dosage form. The only observable difference is for the Food Chopper where the early time points have a slower release for (outside lab) compared to Collegium. The firm explained it as due to higher variability (standard deviation) of the sample particle size between replicates. For example, the standard deviation reported by (outside lab) at the 15 minute time point for 6 tablet replicates was 21.4%, whereas Collegium reported only 4.8% RSD at the same time point.

B. DETERx Capsules
The percentage recovery between the two labs differ by less than one percent for each PSR technique.

None of the three techniques used were effective in significantly defeating the extended release properties of the drug product. The rank order of the dissolution profiles is also the same where both the Food Chopper and Coffee Grinder give similar profiles that are slightly faster than the control and the Mortar and Pestle is the most effective technique in altering the extended release properties of DETERx.

Evaluation: Noted. The results obtained by the two laboratories were in acceptable agreement as stated by the applicant. Although most of the compared procedures are well defined by method parameters used, there are several procedures that can be affected by individual analyst. Those include grinding with a mortar and pestle, fine grating and the use of tablet crusher.

**Reviewer’s Assessment:**
The abuse deterrence studies included in this section provided an overview of the product’s capability of abuse deterrence and how it compares with the already approved abuse deterrent product Oxycontin® as well the non-abuse deterrent Roxicodone tablets.

The abuse deterrence studies and results summarized above indicate that in most of the tests the study drug DETERx demonstrated better or comparable in vitro abuse deterrent properties. Note that no product is completely immune from sophisticated abuse. The final acceptability of the abuse deterrent properties is evaluated by the Controlled Substance Staff Dr. James Tolliver).
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/s/

JAMES M TOLLIVER
09/09/2015

MICHAEL KLEIN
09/09/2015
CLINICAL INSPECTION SUMMARY

DATE: September 4, 2015

TO: Ayanna Augustus, Ph.D., Regulatory Project Manager
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    Ellen Fields, M.D., Team Leader
    Division of Analgesia, Anesthesia, and Addiction Products

FROM John Lee M.D., Medical Officer
    Good Clinical Practice Assessment Branch
    Division of Clinical Compliance Evaluation
    Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
         Kassa Ayalew, M.D., M.P.H., Branch Chief
         Good Clinical Practice Assessment Branch
         Division of Clinical Compliance Evaluation
         Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 208090

APPLICANT: Collegium Pharmaceutical, Inc.

DRUG: Oxycodone Extended-Release Capsules (Xtampza®)

NME: No

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

REVIEW CLASSIFICATION: Standard

DARRTS CONSULTATION DATE: March 3, 2015

INSPECTION SUMMARY GOAL DATE: September 7, 2015

REGULATORY ACTION GOAL DATE: October 9, 2015

PDUFA DUE DATE: October 12, 2015
I. BACKGROUND

In this NDA 208090, Collegium Pharmaceutical, Inc. (Collegium) references NDA 22272 for OxyContin® in seeking 505(b)(2) approval of Xtampza® (trade name pending), an oxycodone formulation engineered as microspheres in capsule for extended abuse-deterrent analgesia. Collegium’s proposed indication for use for Xtampza® is identical to that for OxyContin®, management of severe pain requiring continuous long-term opioid use for which alternative treatment options are inadequate.

Of the studies sponsored by Collegium (under IND 75786) in support of this NDA, the core efficacy Study CP-OXYDET-08 and the human abuse liability (HAL) Study CP-OXYDET-24 were identified for audit at good clinical practice (GCP) inspections of four clinical investigator (CI) sites. The two studies are described below as applicable to the GCP audit.

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

This double-blind, placebo-controlled, randomized withdrawal study was conducted between August 2012 and July 2014 in 389 randomized subjects (46 CI sites) with moderate/severe chronic low back pain (CLBP) requiring the around-the-clock (ATC) use of an opioid analgesic. The primary study objective was to determine the efficacy of Xtampza® in opioid-experienced and opioid-naive subjects with CLBP.

The study consisted of four periods, total duration of up to 24 weeks: (1) screening, up to four weeks; (2) open-label dose titration, up to six weeks; (3) double-blinded randomization and dose maintenance, 12 weeks; and (4) safety follow-up, two weeks. Using an e-diary, subjects completed daily a numerical rating scale (NRS) for pain, from the start of open-label dose titration through end of study.

Subject Selection

- Age 18-75 years, moderate or severe CLBP for at least six months, on analgesic medication with 24-hour pain intensity score 5-9 (inclusive) on 11-point NRS, and qualified for ATC opioid use
- CLBP per Quebec Task Force Scale (QTFS): (1) non-malignant and non-neuropathic, Class 1 or 2; (2) neuropathic, Class 3; or (3) symptomatic for at least six months after back surgery, Class 9
- For opioid-naive subjects, need for opioid medication and failed (NRS pain score ≥ 5) acetyl-para-aminophenol (APAP, acetaminophen) and/or non-steroidal anti-inflammatory drug (NSAID)
- Prior to dose titration: (1) average of NRS pain scores at Visits 1 and 2 between 5 and 9 (inclusive); (2) discontinuation of all prohibited medications for at least seven days
- Prohibited therapies: discontinuation of any non-exceptioned analgesic and/or local pain treatment (e.g., nerve block); unchanged adjunct therapy for at least four weeks (e.g., physical therapy)
- Prior to randomization: last six weeks, study medication 20-80 mg every 12 hours; last seven days, adequate pain control (NRS score ≤ 4 and ≥ two points below screening score; APAP ≤ 2000 mg)

Treatment Groups and Regimen

- Open-label titration of Xtampza® to stable, subject-specific, daily oral regimen of 20-160 mg, then blinded randomization in equal ratio to: (1) continued Xtampza®, or (2) placebo.
- Placebo group: dose taper to avoid opioid withdrawal, stepwise dose reduction every five days (up to 20 days) with use of rescue APAP as needed for breakthrough pain (BTP)
- Rescue APAP for BTP: one or two tablets (500 or 1000 mg) every four to six hours, not to exceed four tablets (2000 mg) in any 24-hour period
Major Study Endpoints and Analyses

- Primary: mean change in NRS pain score (last seven days) from randomization to blinded Week 12
- Short Form 12-version 2-Item Health Survey (SF-12v2): self-report of general quality of life
- Roland-Morris Disability Questionnaire (RMDQ): self-report of physical disability caused by CLBP
- Patient Global Impression of Change (PGIC): self-report of pain-related change in activity
- Total amount of rescue medication used for BTP
- Time-to-exit (TTE): days from randomization to discontinuation (censored at study completion)
- Adverse events (AEs), physical exam and vital signs, laboratory testing, electrocardiogram (ECG)
- Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS)

Sponsor-Reported Outcomes

- Primary endpoint and analysis: Marginal mean change (weighted for treatment duration) in PI-NRS score was greater for Xtampza® relative to placebo (p < 0.0001). Significant improvement in pain intensity was observed by blinded treatment Week 2 (and sustained throughout study).
- Primary analysis results were supported by those of secondary and sensitivity analyses: statistically significant greater efficacy for Xtampza® relative to placebo for SF-12v2 (some measures), PGIC, rescue medication use, TTE, and weekly pain scores.
- Observed Xtampza® AE profile was consistent with those of other opioids in the same pharmacological class. Xtampza® was well-tolerated with no new safety concerns identified. Treatment compliance was consistently high (> 97%) throughout all study phases.

Study CP-OXYDET-24

Xtampza® was called Oxycodone DETERx® in the original protocol for Study CP-OXYDET-24 entitled: Assessment of the Oral Human Abuse Potential of Oxycodone DETERx®

This randomized, controlled (active and placebo), double-blind, crossover HAL study was conducted between January and June of 2014 in 111 healthy recreational opioid users enrolled at a single US CI site. The primary study objective was to evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) indicative of abuse potential for intact and chewed Oxycodone DETERx 40 mg (DETERx) relative to crushed and dissolved oxycodone IR 40 mg.

The 12-week study consisted of: (1) subject screening (Visit 1), three weeks; (2) double-blinded qualification (Visit 2, naloxone challenge and drug discrimination), one week; (3) double-blinded six-way crossover treatment (Visits 3-8), seven weeks; and (4) safety follow up (Visit 9), one week. Of the 111 subjects enrolled, 63 were randomized and treated (blinded crossover), and 38 completed the study.

Subject Screening

Rigorous criteria defined a subject population enriched for subject safety and/or euphoric PD response. Minor deviations from those criteria likely to favor a negative study outcome (and therefore unfavorable for NDA approval) were not rigorously cited. The major subject selection criteria are described below.

Inclusion Criteria

- Adult (age 18-55 years) recreational, non-dependent and non-tolerant opioid user in good health, with overall frequency of opioid use ≥ 10 times within last year and at least once within last 12 weeks
- Not opioid dependent or tolerant per Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-IV-TR), no treatment for addiction, no dietary restrictions, can tolerate oxycodone 40 mg, and able to eat a high-fat high-calorie meal (HFHC) within 20 minutes
- At screening and periodically throughout study: negative urine drug screen (UDS) except for tetrahydrocannabinol; negative alcohol breath test
Exclusion Criteria

- Any clinically significant condition (all organ systems), including any condition that may interfere with drug PK; drug and/or alcohol dependence (except caffeine and nicotine) per DSM-IV-TR criteria
- Any contraindication to opioid use (respiratory depression, asthma, hypercarbia, paralytic ileus); pregnant or nursing women, body mass index (BMI) > 33.0 kg/m²
- Heavy smoker, user of chewing tobacco or nicotine patch, or unable to abstain from smoking for at least five hours; hypersensitivity to any of the test products or their ingredients; positive serology for human immunodeficiency virus (HIV), hepatitis B (surface antigen), hepatitis C (antibody)

Subject Qualification

Following screening, subjects were tested for lack of potential for opioid withdrawal and for drug responsiveness and tolerance. Subjects proceeded to blinded crossover treatment upon a showing of acceptable: (1) testing results for naloxone challenge and drug discrimination; (2) study medication tolerance (including no emesis within six hours); and (3) general behavior predictive of study completion.

- **Naloxone Challenge:** This screening test was to minimize the potential for opioid withdrawal during blinded crossover treatment. All subjects initially received 0.2 mg of intravenous (IV) naloxone. If no withdrawal signs were seen (COWS score ≤ 5), an additional 0.6 mg was given. If again no withdrawal signs were seen, the subject proceeded to be evaluated for drug discrimination.

- **Drug Discrimination:** This screening test was to confirm the subject’s ability to distinguish placebo from crushed dissolved oral (PO) oxycodone IR 20 mg for PD effects indicative of abuse potential.
  - Fasting (≥ 10 hours) subjects were randomly given (double-blinded) either the test medication or placebo on Day 1, and the alternate study medication on Day 2 (at least 24 hours after Day 1).
  - Subjects were evaluated pre-dose and up to five hours post-dose using the drug effects questionnaire (DEQ) for Drug Liking to determine qualification for blinded crossover treatment (unblinded results).
  - Acceptable results were: (1) following oxycodone IR dosing, minimum peak score ≥ 65; (2) within two hours of oxycodone IR dosing, at least 15-point higher peak (relative to placebo) in visual analog scale (VAS) score; and (3) following placebo dosing, VAS score between 40-60 (inclusive).

Blinded Crossover Treatment (Visits 3-8)

A total of six study medications were used in this study. Six different combinations of study medications and fasting states defined six treatment regimens. Subjects were randomized in equal ratio to one of six double-blinded treatment groups, each with different crossover schedules for the six successive treatment regimens separated by a minimum of five washout days. The unblinded pharmacist prepared the study medications according to the 6 x 6 Williams randomization code.

Subjects took single doses of three (of six) study medications, either fed or fasting for ≥ 10 hours (eating not allowed for four hours after, water not allowed from one hour before to one hour after). Non-study medications were limited to oral APAP (≤ 1.0 g/day) and hormonal contraceptives.

**Study medications**

Intact DETERx, chewed DETERx, and oxycodone IR (each with matching placebo)

**Treatment regimens**

- A (fed) and B (fasting): intact DETERx, placebo for chewed DETERx, and placebo for oxycodone IR
- C (fed) and D (fasting): chewed DETERx, placebo for intact DETERx, and placebo for oxycodone IR
- E (positive control, fasting): oxycodone IR and two placebos (for intact and chewed DETERx)
- F (negative control, fed): three placebos (for intact and chewed DETERx, and for oxycodone IR)
Treatment sequences
- Group 1: Regimens A, B, F, C, E, D
- Group 3: Regimens C, D, B, E, A, F
- Group 4: Regimens D, E, C, F, B, A
- Group 5: Regimens E, F, D, A, C, B
- Group 6: Regimens F, A, E, B, D, C

Major Study Endpoints and Analyses
- Co-primary analyses: pair-wise comparisons of the mean peak effect ($E_{\text{max}}$) for Drug Liking, among:
  - Crushed oxycodone IR fasting (positive control Regimen E)
  - Chewed DETERx fed (Regimen C)
  - Chewed DETERx fasting (Regimen D)

  A comparison of the positive control Regimen E with the negative control Regimen F (fed placebos) served as the validation for Regimen E as an appropriate positive control.

- Primary DEQs: one bipolar VAS for Drug Liking and eight unipolar VAS for Feeling High, Any Drug Effect, Good Effects, Bad Effects, Feel Sick, Nausea, Sleepy, and Dizzy
- Additional questionnaires: Overall Drug Liking, Addiction Research Center Inventory-Morphine Benzedrine Group (ARC1MBG), Take Drug Again, and Price Value

  Pre-dose evaluations were limited to Nausea, Feel Sick, ARC1-MBG, and pupillometry. DEQs were assessed post-dose at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours. Take Drug Again and Overall Drug Liking were assessed at eight and 24 hours post-dose, and Price Value was assessed at 24 hours. Calculated PD parameters included: $E_{\text{max}}$, area under the effect curve (AUE), time to maximum effect ($T_{E_{\text{max}}}$), and mean observed effect ($E_{\text{mean}}$).

- PK endpoints: For each blinded crossover treatment, serial blood samples were assayed pre-dose and post-dose at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours.

- Pupillometry: pupil diameter measured (using NeurOptic® VIP-200 pupillometer) on the same eye under controlled conditions for each blinded crossover treatment, pre-dose and post-dose at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours

- Safety endpoints: clinical AEs, laboratory data (chemistry, hematology, UDS), vital signs, pulse oximetry for hemoglobin oxygen saturation ($SpO_2$)

Sponsor-Reported Outcomes
- Relative to crushed dissolved PO oxycodone IR, the $E_{\text{max}}$ VAS score for Drug Liking was lower for both intact and chewed DETERx (fed or fasting), suggesting lower DETERx abuse potential. Other PD endpoint results supported this primary PD result.

- Assessment validation: Relative to placebo after HFHC, VAS score for Drug Liking of crushed dissolved PO oxycodone IR after fasting was significantly higher, for $E_{\text{max}}$ (LS means of 82 and 55 mm, $p < 0.0001$) and for all AUE measures ($p < 0.0001$).

- The PK profiles ($C_{\text{max}}$ and AUC) of chewed and intact DETERx (fed or fasting) were similar and supportive of similar bioequivalence without dose dumping after chewing.

- DETERx was well tolerated by subjects, either taken intact or chewed. The observed DETERx safety profiles (intact or chewed) were similar and consistent with that expected for an opioid product. Chewing DETERx did not increase the incidence of AEs.
II. INSPECTIONS

For Study CP-OXYDET-08, three CI sites were selected for GCP inspection based on large subject enrollment. For the HAL Study CP-OXYDET-24, the single (only) site was inspected. For both studies, no special concerns were identified for protocol violations, AEs, or CI conflicts of interest.

<table>
<thead>
<tr>
<th>Clinical Investigator</th>
<th>Study, Site, Subjects</th>
<th>Inspection Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Egilius Spierings, M.D. Medvadis Research Corporation 72 Mount Auburn Street Watertown, Massachusetts</td>
<td>Study CP-OXYDET-08  Site 143  12 randomized</td>
<td>April 22 – May 6, 2015 NAI</td>
</tr>
<tr>
<td>2. Samir Azzam, M.D. Global Research 3055 West Orange Avenue Anaheim, California</td>
<td>Study CP-OXYDET-08  Site 133  19 randomized</td>
<td>May 5 - 8, 2015 NAI</td>
</tr>
<tr>
<td>3. Robert Buynak, M.D. Buynak Clinical Research Center 55 University Drive Valparaiso, Indiana</td>
<td>Study CP-OXYDET-08  Site 113  20 randomized</td>
<td>August 24 - 28, 2015 Pending, preliminary NAI</td>
</tr>
<tr>
<td>4. Lynn R. Webster, M.D. PRA Health Sciences 3838 South 700 East Salt Lake City, Utah</td>
<td>Study CP-OXYDET-24  63 randomized and treated (blinded crossover phase)</td>
<td>June 22 – July 10, 2015 Pending, preliminary NAI</td>
</tr>
</tbody>
</table>

NAI = no action indicated (no significant violations); Pending = preliminary communication with field investigator

1. Egilius Spierings, M.D

   a. What was inspected:

      Records review: Institutional review board (IRB) oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records

      Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification

      Data verification: randomization, major efficacy endpoints (including SF-12v2), AEs, protocol deviations, subject discontinuations, and concomitant medication use

   b. General observations and comments:

      Study CP-OXYDET-08, Site 143: 34 subjects were screened, 24 were enrolled (10 screen failures), 12 were randomized (12 titration failures), and 8 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for the 12 randomized subjects.

      No significant deficiencies were observed for the CI site and a Form FDA 483 was not issued. Uncited observations included an error in the NDA in presenting the SF-12v2 data (minor endpoint, audited at inspector discretion), verbally discussed with the CI as a deficiency for the sponsor.
• The source data (screening and/or e-diary data) for the SF-12v2 questionnaire (non-primary endpoint data) appeared to be discrepant from the data reported in the NDA (reverse scoring: 1=5, 2=4, 3=3, 4=2, 5=1) for the following four questionnaire items (% of 37 evaluations, 12 subjects): 1 (32%), 5 (57%), 6A (81%), and 6B (54%).

• This apparent data discrepancy (source versus NDA) was discussed with the sponsor (May 20, 2015), who clarified that: (1) the raw data for the four items had been recoded to facilitate data analysis, as reported in Section 15.3 of the Statistical Analysis Plan (SAP); and (2) the recoded NDA data (Listing 16.2.6.2.1) was mislabeled in the NDA as raw data.

• The recoded NDA data were consistent with the source data when considered according to the recoding scheme presented in the SAP of the NDA. In follow up of this post-inspection correspondence, the sponsor amended the NDA to correct this error (SN 0020; May 28, 2015).

All observations were consistent with adequate study conduct, including GCP-compliant data management (at the CI site and by the sponsor), informed consent, AE monitoring and reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well organized and appeared complete. All audited data were verifiable among source records, case report forms (CRFs), and NDA data listings (amended, as applicable).

c. Assessment of data integrity: The data from this study site appear reliable.

2. Samir Azzam, M.D.

a. What was inspected:

Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records

Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification

Data verification: randomization, study medication kit assignment, primary efficacy endpoint (pain reduction), AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study CP-OXYDET-08, Site 133: 37 subjects were screened, 25 were enrolled (12 screen failures), 19 were randomized, and 14 completed the study (five discontinued). Case records were reviewed for all enrolled subjects, including detailed review for 12 randomized subjects. No significant deficiencies were observed and a Form FDA 483 was not issued.

• The only deficiency observed was one isolated instance of not performing the protocol-specified urine drug screening test at subject screening. This protocol deviation had been reported to the sponsor, and subsequently in the NDA as a minor protocol deviation (unlikely to be significant).

• Verification of subject randomization was completed at OSI review of the establishment inspection report (EIR), by comparing the study kit numbers (collected at inspection) against an unblinded key that correlates the kit numbers with subject identification numbers (NDA Amendment 19, submitted by sponsor upon OSI request).

Overall, study conduct appeared adequate, including for informed consent, AE monitoring and reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.
3. Robert Buynak, M.D.

a. What was inspected:
   Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
   Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
   Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:
   Study CP-OXYDET-08, Site 113: 37 subjects were screened, 29 were enrolled, 20 were randomized, and 12 completed the study. Case records were reviewed for all subjects, including detailed review for 20 subjects (ten randomized, two not randomized, and eight screen failures).
   No significant deficiencies were observed and a Form FDA 483 was not issued. Deficiency observations were limited to three minor isolated errors in documenting otherwise adequate drug accountability. The recordkeeping deficiencies appeared unlikely to be significant (not cited or verbally discussed). Study conduct appeared adequate, including IRB and sponsor oversight of study conduct. Study records were well organized and appeared complete. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

4. Lynn R. Webster, M.D.

a. What was inspected:
   Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
   Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
   Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:
   Study CP-OXYDET-24: 206 subjects were screened, 107 were enrolled (blinded subject qualification phase), 63 were randomized and treated (blinded crossover treatment phase), and 38 completed the study. The major reasons for not completing the study (25 subjects) were: withdrawal of consent, subject non-compliance, and emesis after dosing. Records were reviewed for all randomized subjects, including detailed review for ten subjects.
   No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were adequately organized and appeared complete. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.
III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Collegium submitted this NDA 208090 for Xtampza® as a 505(b)(2) application, with OxyContin® as the reference listed drug. Xtampza® is a new oxycodone formulation engineered as microspheres (in capsule) for extended abuse-deterrent analgesia in managing severe pain requiring continuous long-term opioid use. Of the new studies sponsored by Collegium, the core efficacy Study CP-OXYDET-08 and the HAL Study CP-OXYDET-24 were audited at GCP inspections of four CI sites.

- Study CP-OXYDET-08 was a double-blind, placebo-controlled, randomized withdrawal study conducted between 2012 and 2014 in 389 subjects with CLBP randomized at 46 CI sites. Open-label dose titration preceded double-blinded randomization into active or placebo maintenance pain management. Subjects recorded pain intensity daily from the start of open-label through end of study. For the on-site audit of this study, three of the 46 CI sites were selected based on large subject enrollment. At the three CI sites combined, 51 subjects were randomized (13%), of whom case records for 34 subjects (9%) were reviewed in detail.

- Study CP-OXYDET-24 was a double-blind, placebo/active-controlled, randomized six-way crossover HAL study conducted over six months in 2014 in 63 healthy volunteers (recreational opioid users) randomized/treated at a single CI site. Double-blinded subject qualification (for opioid withdrawal and discrimination) preceded double-blinded randomization into one of six sequences of otherwise identical crossover treatments (six abuse scenario variations). Subjects were evaluated for their perception of euphoria and other opioid effects after each treatment. For the on-site audit of this study, case records for all subjects were reviewed, including detailed review for ten subjects (16%).

At all four study-sites, no significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequately GCP-compliant, including IRB/sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the four study-sites appear reliable as reported in the NDA.

Note: For two sites (see Section II), the EIR has not been received from the field office and the final inspection outcome remains pending. Upon completion of EIR review, an addendum to this inspection summary will be forwarded to the review division if the final outcome changes from that reported. Close-out correspondence with each CI (copied to review division) otherwise indicates EIR review completion without new significant findings and outcome finalization as reported in this summary.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Reference ID: 3816248
{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JONG HOON LEE  
09/04/2015

JANICE K POHLMAN  
09/04/2015

KASSA AYALEW  
09/06/2015

Reference ID: 3816248
1 PURPOSE OF MEMO

In preparation for an upcoming Advisory Committee meeting, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we comment on the potential effectiveness of packaging, approved labeling, and other written materials to mitigate the risk of administering Collegium’s extended-release oxycodone product incorrectly on an empty stomach.

2 OVERALL ASSESSMENT

2.1 INTRODUCTION

Collegium’s extended-release oxycodone product must be administered with food to ensure plasma levels are consistent and similar to plasma levels seen with the administration of
OxyContin (oxycodone hydrochloride). Co-administration of Collegium’s product with food increases the extent of absorption when compared to administration of the same drug in the fasted state. The requirement for Collegium’s product to be administered with food is different than almost all other oral opioid products that can be administered without respect to food, the exception being Opana ER, which should be taken on an empty stomach. We searched for data in FDA’s adverse event database and the literature to determine if patients are counseled about this food effect when taking Opana ER, or if errors are occurring when administering the product. We did not find any information to suggest that this is occurring, but it is important to note that the absence of reports does not provide assurances that such errors are not occurring. Under-reporting of adverse events and medication errors are a known phenomenon, and thus it could be the case that the administration errors with Opana ER are occurring but not reported.\(^1\) Also, the significance of the food effect with Opana ER is less substantial than Collegium’s product. With Opana ER, there is about a 50% increase in the fed \(C_{\text{max}}\) versus the fasted \(C_{\text{max}}\).\(^2\) There can be a nearly 100% difference between \(C_{\text{max}}\) levels when Collegium’s extended-release oxycodone product is taken without food versus when taken with food (31.46 ng/mL fasted vs. 58.01 ng/mL with a medium fat meal).\(^3\)

Because of significant variations in plasma levels based on administration with or without food, inappropriate administration of Collegium’s oxycodone product without food will result in an under-dose, which may lead to inadequate pain control for the patient. An additional concern is that patients who experience inadequate pain control may take additional drug in an effort to achieve adequate pain control. For example, unaware of the important food effect, the patient takes a prescribed dose of this product on an empty stomach and does not feel the medication is effective enough at the prescribed dose to treat their pain. The patient then decides to take an additional capsule to improve pain relief. If the additional medication is given while the patient coincidentally takes it with food, especially a medium-fat meal, the patient’s plasma levels could be significantly increased, leading to high serum plasma levels and potentially serious adverse drug events (e.g., respiratory depression). Thus, we are concerned that the differences in absorption resulting from food for Collegium’s product are clinically impactful, and we consider it very important that the medication is consistently taken with food.

To address the significant food effect, Collegium Pharmaceuticals proposes basic labeling statements, such as “Take Collegium Oxycodone capsules with food”. These statements appear in the Dosage and Administration (Section 2.1, 2.5), Clinical Pharmacology (Section 12.3), and the Patient Counseling Information (Section 17) sections of the Prescribing Information and in

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the Medication Guide. We note that, in general, the remainder of the proposed labeling is similar to the rest of the Extended-Release and Long-Acting (ER/LA) opioid analgesics class, and that the other products generally can be taken without regard to food in most circumstances. Based on patient and provider familiarity with the administration requirements of other opioid products, we have concern that confirmation bias could predispose prescribers and patients to mistakenly believe that this particular ER opioid analgesic can be taken without regard to food.

To provide input on this subject, DAAAP has consulted us to comment on the effectiveness of labeling to convey critical drug administration information in a situation where the proposed administration is different than almost all other drugs in the same class and given the marketing history with other extended-release oxycodone products. We note there are currently two other ER/LA oxycodone products with abuse deterrent properties that are currently approved (Oxycontin and Targiniq), neither of which have a food effect.

2.2 ANALYSIS ON THE EFFECTIVENESS OF COUNSELING, LABELING, AND OTHER WRITTEN MATERIALS

It is very important that critical information is consistently communicated to new patients who have opioid products prescribed for them, or patients being switched between different ER/LA opioid products. This communication can generally occur in two ways. First, the information can be communicated verbally via healthcare providers and secondly it can also be communicated through written material. With respect to the effect of food on this product, given that ER/LA opioids historically can be taken without regard to food, we have concern that some healthcare providers may forget to include this information when counseling patients on this proposed product. Similarly, patients who have been on other ER/LA opioids may not read the written material for this proposed product because they feel they are already well-educated on ER/LA opioids. Thus, if the patient is not counseled on this or does not read the important information in the medication guide, there is risk for patients to take the medication without food. Lastly, even if a patient is told or reads that the product should be taken with food, there remains a risk that such instructions may not be followed if the patient does not comprehend the significance of this advice.

To identify the consistency in which important information is communicated through counseling and written labeling material read by the patient, we searched the literature to determine whether such communication and reading of the label routinely occurs in the opioid-patient population, and whether this would be expected to result in behavior change and proper medication use. In our search, we focused on the opioid class of drugs and this patient population to eliminate the potential for differences in counseling and patient behavior with other chronic disease states.

We identified one article meeting these criteria. This article examined the frequency of counseling provided by health care practitioners (HCPs) in patients prescribed acetaminophen containing opioids. In this article, 149 patients from either an urban academic emergency
department in Chicago, Illinois or an outpatient pharmacy at a public hospital in Atlanta, Georgia were enrolled in the study. Patients were interviewed to assess their recall of counseling by their physician, nurse, and pharmacist upon receiving a new prescription. The results indicated that patients were provided details of administration by either a physician/nurse or pharmacist 49.7% of the time (44.3% + 5.4%, respectively). Importantly, the results of the article suggest that half of patients do not recall receiving counseling on the administration techniques of opioid products. We note that this study was conducted in only two locations (both in an urban setting) and that the medications studied were generally short-acting opioids containing acetaminophen which are not subject to the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA REMS) program, which could limit the generalizability of the findings to Collegium’s product to some extent since this would be subject to the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA REMS) program. Further, the study did not examine whether the counseling provided by the health care practitioner on administration translated to changes in patient behavior or an intention to change patient behavior with proper medication use among those users who did receive counseling. Lastly, the study measured patient recall of counseling which could differ from the patient actually having received counseling. Notwithstanding these limitations, this study suggests that many patients are unlikely to be counseled on the administration of Collegium’s opioid product.

We also considered additional information collected from the ER/LA REMS program. Specifically, the Division of Risk Management (DRISK) reviewed patient survey data submitted as part of an assessment of the ER/LA REMS on February 26, 2015. The patient survey was conducted in 413 patients who were deemed eligible to participate if they were adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesic between December 1, 2012 and November 30, 2013. The surveys included an assessment of the rate in which patients received the corresponding medication guide and patient counseling document (PCD), when first prescribed an ER/LA opioid analgesic.⁵ According to DRISK’s review, for the medication guide, 90% of patients received them from the pharmacy. However, approximately 19% (16%+3%) of patients either did not read the medication guide, or only read some of it (Table 1). For the PCD, a document that prescribers may use to counsel patients about important safety information, the responses indicated that over 60% either did not receive it or were not sure if they received it (see Table 1).


### Table 1 - Selected Results of DRISK’s Review of ER/LA REMS Patient Survey

<table>
<thead>
<tr>
<th>Read medication guide</th>
<th>Never read any: 14 (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Read some, at least once: 64 (16%)</td>
</tr>
<tr>
<td></td>
<td>Read all, at least once: 274 (66%)</td>
</tr>
<tr>
<td></td>
<td>Read all, with each pharmacy fill: 61 (15%)</td>
</tr>
<tr>
<td></td>
<td>Refused: 0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Received Patient Counseling Document from healthcare provider when first prescribed the current ER/LA opioid analgesic</th>
<th>Yes: 155 (37%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No: 135 (33%)</td>
</tr>
<tr>
<td></td>
<td>Not sure: 123 (30%)</td>
</tr>
<tr>
<td></td>
<td>Refused: 0 (0%)</td>
</tr>
</tbody>
</table>

The survey also included an assessment of patient comprehension of five key risk messages of ER/LA opioid analgesic products. DRISK concluded that there was generally a high understanding of key risk messages related to the product class. However, some information had a lower understanding of aspects of safe storage and using the drug safely. This suggests that not all important information is consistently recalled by patients receiving new prescriptions of ER/LA opioid analgesics. Though most of the survey data were encouraging regarding patient knowledge, DRISK noted that the survey population was not representative of the opioid user population (e.g., primarily younger, commercially insured patients represented in the survey), and recommends caution when applying these results to the actual drug use population.

Packaging and patient information labeling is often used to improve recall of and adherence to important prescribing information conveyed by healthcare professionals. However, from a failure mode perspective, patient information labeling is not a fail-safe measure because there is no way to ensure that the label is read, understood, or likely to be attended to. Thus, there is no way to determine without further data that the proposed labeling for the Collegium product is a mechanism that will ensure that patients will correctly administer the drug on a consistent basis. In our view, it is likely that labeling can be expected to incrementally address the risks related to incorrect administration, but there are residual risks even with labeling interventions. We are unable to determine the extent of the residual risk without further data. Such data could be collected by Collegium from a risk analysis to examine the severity of the risk and the

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probability that it will occur in order to determine what failure mode strategies should be put in place to mitigate the risk.\(^7\)

We note there are other products that must be taken with food or on an empty stomach that have administration instructions addressed via labeling. However, the benefit-risk profile for these drugs may be quite different than opioids and this should be taken into account. The risk for variance in the absorption and plasma levels if a product is not taken correctly with respect to food should be weighed against the risk for incorrect use/medication errors and resulting adverse drug events.

2.3 EFFECTIVENESS OF PACKAGING

We considered packaging of products that require administration with food to prevent wide variations in plasma concentrations, and found that some use a unit-of-use packaging configuration. This type of packaging allows the food statement to be prominently displayed to the end user at the time of administration. Collegium has proposed marketing this product in 100-count bottles only, which are not unit-of-use, and therefore unlikely to be dispensed directly to patients. Thus, Collegium has lost an important opportunity to convey information directly to patients. Unit- of- use packaging can provide a durable approach to help ensure that patients see the proper administration instructions at the time that each dose is administered.

We identified two products that have significant food-effects that use packaging to address the administration requirements. These two products are packaged in unit-of-use containers that are expected to be dispensed directly to patients and, thus, help to ensure that the patient would see the administration instructions for each dose. For one of the products, an HIV medication which should be taken with food, DMEPA has not received any reported medication errors related to administration on an empty stomach as of May 15, 2015.

However, the second product, an oral chemotherapy, did have medication errors (23 non-serious cases) related to the unit-of-use packaging. Root cause analysis of the errors found that they were likely caused by an ambiguous food graphic (a circle that included a fork and knife with a line through them) and the use of the negative statement “Do not take with food”. There is post-marketing experience from other drug products that suggest patients and providers have a tendency to overlook the word “Not” in negative statements, and thus misinterpret the directive as a positive statement.\(^8\) In this particular instance, patients may overlook the “not” and incorrectly interpret that their medication should be taken with food. Additionally, prior to implementation, the food graphic was not tested and validated to ensure that patients generally understood what the food graphic was trying to communicate. The Sponsor for the oral chemotherapy product removed the food graphic and revised the negative statement to a positive statement – “Take on an empty stomach” to remove the source of

\(^7\) Ibid.

confusion and mitigate the risk. Since September 27, 2013, the supplement approval date, we have received only one FAERS case attributed to the revised packaging. By comparison, in the 26-month period prior to the labeling revision, we received 23 cases of administration errors where this product was taken with food.

The experience with the oral chemotherapy product demonstrates that even though unit of use packaging can be helpful to reduce error risks, there may still be residual risk to the patient if the statements are not designed well. If unit of use packaging is considered during product development, the Sponsor would need to take into consideration packaging configurations that would be appropriate for the various patient regimens (i.e., acute treatment for 5 to 10 days versus longer term use of the product). They would have to overcome technical challenges that arise for the range of dosing and day supply for various patient regimens and when dispensing a controlled substance. To ensure that the packaging is optimized to provide a clear and consistent statement to the patient and is feasible for all patient regimens, a comprehensive risk analysis and labeling comprehension study should be conducted to ensure that the administration requirements are followed and risks associated with not following directions are clear to patients.

In addition to having a positive statement “take with food” on the unit- of- use package, one such approach that can improve adherence is to utilize warning information on written materials, packaging and labeling that fully characterizes the severity of the hazard. The greater the perceived hazard, the more responsive people will be after reading warnings. It is important to note, that developing such packaging would require additional manufacturing controls data and human factors study data.

Lastly, these packaging strategies described above, even if feasible to implement for this product, can remind or direct a patient to the correct behavior, which is useful, but ultimately may not prevent the wrong behavior. It is important therefore to acknowledge that even with a unit-of-use packaging approach there remains some residual risk and that administration errors will likely still occur.

2.4 CONCLUSION

After considering the above information in totality, we conclude that there is some risk that patients will administer this product incorrectly. Further, the proposed packaging and labeling by the Sponsor is inadequate to eliminate the possibility of an administration error with their oxycodone product. The severity of outcome related to taking Collegium’s product inconsistently or incorrectly with respect to food should be carefully considered in the overall evaluation of this product’s risks.

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If DAAAP determines that the benefits outweigh the risks, we recommend that Collegium study the feasibility of using unit-of-use packaging to partially address the risk of administration errors.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES H SCHLICK
09/03/2015

BRENDA V BORDERS-HEMPHILL
09/03/2015

IRENE Z CHAN
09/03/2015

TODD D BRIDGES
09/03/2015

Reference ID: 3815056
Date: March 3, 2015

To: Ni Aye, Khin, M.D., DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Kassa Ayalew, M.D.,M.P.H., Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Thompson, M.D. Team Leader, GCPAB
CDER OSI PM Track
John Lee
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Steven Galati, MD Medical Officer, Division of Anesthesia, Analgesia, and
Addiction Products (DAAAP)
Ellen Fields, MD, Clinical Team Leader, DAAAP

From: Ayanna Augustus, PhD, RAC, Regulatory Health Project Manager, DAAAP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA - 208090
IND#: 75786
Applicant/ Applicant contact information (to include phone/email):
Alison B. Fleming, PhD / VP, Product Development
780 Dedham Street, Suite 800 / Canton, MA 02021
Phone 781.713.3724 / Fax 781.828.4697
afleming@collegiumpharma.com
Drug Proprietary Name: Xtampza ER
Generic Drug Name: oxycodone extended-release capsules
NME or Original BLA (Yes/No/Not Applicable*): No
Application Submission Date: 12/12/14
Review Priority (Standard or Priority or Not Applicable*): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No/Not Applicable*): No
*For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate

**PDUFA: 10/12/15**
**Action Goal Date: 10/9/15**
**Inspection Summary Goal Date: September 7, 2015**

## II. Protocol/Site Identification

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).*

<table>
<thead>
<tr>
<th>Site # (Name, Address, Phone number, email, fax#)</th>
<th>Protocol ID</th>
<th>Number of Subjects</th>
<th>Indication/Primary endpoint and other endpoints for verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynn R. Webster, MD, PRA Healthsciences, Salt Lake City, Utah</td>
<td>CP-OxyDET-24</td>
<td>36 completed subjects</td>
<td>Emax of Drug liking is primary endpoint: Between chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted and between chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted</td>
</tr>
</tbody>
</table>
| Study contact: Melinda O’Connor, BA  
Telephone: 781-713-3729  
Facsimile: 781-828-4697  
E-mail: moconnor@collegiumpharma.com | CP-OXYDET-08 | 19 | Primary endpoint: Average pain intensity change from baseline to week 12.  
Secondary: PGIC, total rescue, quality of life, time to exit |
| Site ID-133 (Samir Azzam, Global research, 3055 West Orange Avenue, Suite 201 Anaheim, California 92804)  
P: 714-220-1251  
F: 714-220-1250 | | | |
### Site Selection/Rationale

The clinical sites were chosen using the site selection tool. Additionally, a site assessing the human abuse liability (HAL) study to be analyzed in consultation with the CSS Division was chosen. The product is an abuse deterrent formulation of an extended-release opioid. The Division has decided that the HAL study/studies have significant weight in the decision making of a NDA’s approval. Therefore, a site should be evaluated where an HAL study was completed.

#### Domestic Inspections:

Reasons for inspections (please check all that apply):

- **X** Enrollment of large numbers of study subjects
- _____ High treatment responders (specify):
- **X** Significant primary efficacy results pertinent to decision-making
- _____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- _____ Other (specify):

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### Site # (Name, Address, Phone number, email, fax#) | Protocol ID | Number of Subjects | Indication/Primary endpoint and other endpoints for verification

| Site ID – 113 (Robert Buynak, Buynak Clinical Research 55 University Drive, Suite 106 Valparaiso, Indiana 46383) | CP-OXYDET-08 | 20 | Primary endpoint: Average pain intensity change from baseline to week 12. Secondary: PGIC, total rescue, quality of life, time to exit |
| Site ID – 143 (Egilius Spierings, Medvadis Research Corporation 72 Mount Auburn Street Watertown, Massachusetts 02472-3930) | CP-OXYDET-08 | 12 | Primary endpoint: Average pain intensity change from baseline to week 12. Secondary: PGIC, total rescue, quality of life, time to exit |
International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Ayanna Augustus, RPM at 301-796-3980 or Steven Galati at 301-796-7408.
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
03/03/2015

STEVEN A GALATI
03/03/2015

ELLEN W FIELDS
03/03/2015
RPM FILING REVIEW
(Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA # 208090</td>
</tr>
<tr>
<td>BLA#</td>
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</tbody>
</table>

Proprietary Name: Xiampza
Established/Proper Name: oxycodone extended-release
Dosage Form: capsules
Strengths: 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg

Applicant: Collegium Pharmaceutical
Agent for Applicant (if applicable):

Date of Application: December 12, 2014
Date of Receipt: December 12, 2014
Date clock started after UN:

PDUFA/BsUFA Goal Date: Oct 12, 2015
Action Goal Date (if different):

Filing Date: February 10, 2015
Date of Filing Meeting: February 5, 2015

Chemical Classification (original NDAs only):
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch

Proposed indication(s)/Proposed change(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative options are inadequate.

Type of Original NDA:
☐ AND (if applicable)
☐ Type of NDA Supplement:
☐ 505(b)(1)
☒ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at: http://inside.fda.gov/ucmg/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499

Version: 12/09/2014

Reference ID: 3701050
Type of BLA

If 351(b), notify the OND Therapeutic Biologics and Biosimilars Team

Review Classification:

The application will be a priority review if:

- A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)
- The product is a Qualified Infectious Disease Product (QIDP)
- A Tropical Disease Priority Review Voucher was submitted
- A Pediatric Rare Disease Priority Review Voucher was submitted

Resubmission after withdrawal? [ ] Resubmission after refuse to file? [ ]

Part 3 Combination Product? [ ]
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

- Convenience kit/Co-package
- Pre-filled drug delivery device/system (syringe, patch, etc.)
- Pre-filled biologic delivery device/system (syringe, patch, etc.)
- Device coated/impregnated/combined with drug
- Device coated/impregnated/combined with biologic
- Separate products requiring cross-labeling
- Drug/Biologic
- Possible combination based on cross-labeling of separate products
- Other (drug/device/biological product)

Yes Track Designation
- Breakthrough Therapy Designation
  (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)
- Rolling Review
- Orphan Designation

PMC response
- PMR response:
  - FDAAA [505(o)]
  - PREA deferred pediatric studies (FDCA Section 505B)
  - Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
  - Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 75786

Goal Dates/Product Names/Classification Properties

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</table>

PDUFA/BsUFA and Action Goal dates correct in tracking system?

If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.

Are the established/proper and applicant names correct in tracking system?

If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name

Version: 12/09/2014
<table>
<thead>
<tr>
<th>Application Integrity Policy</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
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<tr>
<td>If yes, explain in comment column.</td>
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<tr>
<td>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</td>
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<tr>
<td>User Fees</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>✗</td>
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<tr>
<td>User Fee Status</td>
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<tr>
<td>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</td>
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<tr>
<td>Payment for this application (check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>):</td>
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<tr>
<td>Paid</td>
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<tr>
<td>Exempt (orphan, government)</td>
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<tr>
<td>Waived (e.g., small business, public health)</td>
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<tr>
<td>Not required</td>
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<tr>
<td>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</td>
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<tr>
<td>Payment of other user fees:</td>
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<tr>
<td>Not in arrears</td>
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<tr>
<td>In arrears</td>
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<tr>
<td>User Fee Bundling Policy</td>
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<tr>
<td>Has the user fee bundling policy been appropriately applied? If no, or you are not sure, consult the User Fee Staff.</td>
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<tr>
<td>Yes</td>
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<td>No</td>
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<tr>
<td>505(b)(2) (NDAs/NDA Efficacy Supplements only)</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
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<tr>
<td>Is the application a 505(b)(2) NDA? (Check the 350h form,</td>
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</tbody>
</table>

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cover letter, and annotated labeling). If yes, answer the bulleted questions below:

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?  

- Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].

- Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?

If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?  

Check the Electronic Orange Book at:  
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

### Exclusivity

| Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at:  
http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
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</tbody>
</table>

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy.

### NDA/NDAs efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  

If yes, # years requested:  

Note: An applicant can receive exclusivity without requesting it.
There, requesting exclusivity is not required.

| NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use? | | | |
|---|---|---|
| If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? | | | |
| If yes, contact the Orange Book Staff (CDER-Orange Book Staff). | |

BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?

If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM

Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

| Format and Content |
|---|---|---|---|---|
| Do not check mixed submission if the only electronic component is the content of labeling (COL). | All paper (except for COL) | All electronic | Mixed (paper/electronic) | CTD | Non-CTD | Mixed (CTD/non-CTD) |

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?</td>
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<tr>
<td>If not, explain (e.g., waiver granted).</td>
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<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
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<tr>
<td>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</td>
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<table>
<thead>
<tr>
<th>Form</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>Application Form</strong></td>
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<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
<td>☒</td>
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<tr>
<td><strong>Patent Information</strong></td>
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<tr>
<td>(NDAs/NDA efficacy supplements only)</td>
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<tr>
<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
<td>☒</td>
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<tr>
<td><strong>Financial Disclosure</strong></td>
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<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
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<tr>
<td><strong>Clinical Trials Database</strong></td>
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<tr>
<td>Is form FDA 3674 included with authorized signature?</td>
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<tr>
<td>Debarment Certification</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
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<tr>
<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
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</table>

Certification is not required for supplements if submitted in the original application; if foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].

Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”

<table>
<thead>
<tr>
<th>Field Copy Certification (NDAs/NDA efficacy supplements only)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
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</tbody>
</table>

Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR).

If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.

<table>
<thead>
<tr>
<th>Controlled Substance/Product with Abuse Potential</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
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</tbody>
</table>

If yes, date consult sent to the Controlled Substance Staff:

For non-NMEs:
Date of consult sent to Controlled Substance Staff: December 18, 2014

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>PREA</td>
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</tbody>
</table>

Does the application trigger PREA?

If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²

Note: NDAs/BLAs/efficacy supplements for new active ingredients

² [Link](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm)

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(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.

| If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? | ☒ | ☐ | ☐ |
| If no, may be an RTF issue - contact DPMH for advice. | ☒ | ☐ | ☐ |
| If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? | ☐ | ☐ | ☒ |
| If no, may be an RTF issue - contact DPMH for advice. | ☒ | ☐ | ☐ |
| BPCA: | ☒ | ☐ | ☐ |
| Is this submission a complete response to a pediatric Written Request? | ☒ | ☐ | ☐ |
| If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required) | ☒ | ☐ | ☐ |

| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? | ☒ | ☐ | ☐ |
| If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.” | ☒ | ☐ | ☐ |

| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? | ☒ | ☐ | ☐ |
| If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox | ☒ | ☐ | ☐ |

| Prescription Labeling | | Not applicable | | |
| Check all types of labeling submitted. | ☒ | Package Insert (PI) |
| ☐ | Patient Package Insert (PPI) |
| ☐ | Instructions for Use (IFU) |
| ☒ | Medication Guide (MedGuide) |
| ☒ | Carton labels |
| ☐ | Immediate container labels |
| ☐ | Diluent |
| ☐ | Other (specify) |

| YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? | ☒ | ☐ | ☐ |
| If no, request applicant to submit SPL before the filing date. | ☒ | ☐ | ☐ |

---

3 [http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm)

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Reference ID: 3701050
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Is the PI submitted in PLR format?</td>
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<tr>
<td>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</td>
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<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</td>
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<tr>
<td>All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?</td>
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<tr>
<td>MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)</td>
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<tr>
<td>Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?</td>
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<tr>
<td>OTC Labeling</td>
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<tr>
<td>Check all types of labeling submitted.</td>
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<tr>
<td>Outer carton label</td>
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<tr>
<td>Immediate container label</td>
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<td>Blister card</td>
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<tr>
<td>Blister backing label</td>
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<tr>
<td>Consumer Information Leaflet (CIL)</td>
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</tr>
<tr>
<td>Physician sample</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Consumer sample</td>
<td></td>
<td></td>
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<tr>
<td>Other (specify)</td>
<td></td>
<td></td>
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<tr>
<td>Is electronic content of labeling (COL) submitted?</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>If no, request in 74-day letter.</td>
<td></td>
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</tr>
<tr>
<td>Are annotated specifications submitted for all stock keeping units (SKUs)?</td>
<td></td>
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<tr>
<td>If no, request in 74-day letter.</td>
<td></td>
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<tr>
<td>If representative labeling is submitted, are all represented SKUs defined?</td>
<td></td>
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<tr>
<td>If no, request in 74-day letter.</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All labeling/packaging sent to OSE/DMEPA?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Consults</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, specify consult(s) and date(s) sent:</td>
<td></td>
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<td></td>
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<tr>
<td>Meeting Minutes/SPAs</td>
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Reference ID: 3701050
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<tr>
<th>Question</th>
<th>Date(s)</th>
<th>☒</th>
<th>☐</th>
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<tr>
<td>End-of Phase 2 meeting(s)?</td>
<td>March 30, 2010</td>
<td></td>
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<td><strong>If yes, distribute minutes before filing meeting</strong></td>
<td></td>
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<tr>
<td>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</td>
<td>April 16, 2014</td>
<td></td>
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<tr>
<td><strong>If yes, distribute minutes before filing meeting</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any Special Protocol Assessments (SPAs)?</td>
<td>December 1, 2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If yes, distribute letter and/or relevant minutes before filing meeting</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
ATTACHMENT

MEMO OF FILING MEETING

DATE: February 5, 2015

BACKGROUND: 505b2 NDA referencing OxyContin (oxycodone) NDA 22272

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Ayanna Augustus</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Parinda Jani</td>
<td>N</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Ellen Fields</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Sharon Hertz</td>
<td>Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Curt Rosebraugh</td>
<td>N</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Steve Galati</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Ellen Fields</td>
<td>Y</td>
</tr>
<tr>
<td>Social Scientist Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OTC Labeling Review (for OTC products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Microbiology (for antimicrobial products)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Srikant Nallani</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL: Yun Xu</td>
<td>Y</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Reviewer: Kate Meaker</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Freda Cooner</td>
<td>Y</td>
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Reference ID: 3701050
<table>
<thead>
<tr>
<th>Nonclinical (Pharmacology/Toxicology)</th>
<th>Reviewer: Grace Lee</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TL: Dan Mellon</td>
<td>Y</td>
</tr>
<tr>
<td>Statistics (carcinogenicity)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Immunogenicity (assay/assay validation) (for protein/peptide products only)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Product Quality (CMC)</td>
<td>Reviewer: Xiaobin Shen</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Ciby Abraham</td>
<td>Y</td>
</tr>
<tr>
<td>Biopharmaceutics</td>
<td>Reviewer: Fang Wu</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Sandra Suarez</td>
<td>Y</td>
</tr>
<tr>
<td>Quality Microbiology</td>
<td>Reviewer: Erika Pfeiler</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>CMC Labeling Review</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>Facility Review/Inspection</td>
<td>Reviewer: Robert Wittorf</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labels))</td>
<td>Reviewer: James Schlick</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Vicky Borders-Hemphill</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Reviewer: Danny Gozalez</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Kim Lehrfeld</td>
<td>Y</td>
</tr>
<tr>
<td>OC/OSI/DSC/PMSB (REMS)</td>
<td>Reviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TL:</td>
<td></td>
</tr>
</tbody>
</table>
**Bioreresearch Monitoring (OSI)**
- **Reviewer:** John Lee
- **TL:** Janice Pohlman

**Controlled Substance Staff (CSS)**
- **Reviewer:** James Tolliver
- **TL:** Silvia Calderon

**Other reviewers/disciplines**
- **Reviewer:**
- **TL:**

**Other attendees**
- Hina Mehta, Jana Mcaninch, Jana, Josh Lloyd, Youbaud Liu,

**FILING MEETING DISCUSSION:**

**GENERAL**
- **505(b)(2) filing issues:**
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
    - **☐ Not Applicable**
    - **☑ YES ☒ NO**
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?
    - **☐ YES ☐ NO**
  
  **Describe the scientific bridge (e.g., BA/BE studies):**
  - **Two BA studies**

- **Per reviewers, are all parts in English or English translation?**
  - **☒ YES ☐ NO**
  
  **If no, explain:**

- **Electronic Submission comments**
  - **☐ Not Applicable**
  - **☒ No comments**

**CLINICAL**
- **Comments:**
  - **☐ Not Applicable**
  - **☒ FILE**
  - **☐ REFUSE TO FILE**
  - **☐ Review issues for 74-day letter**

- **Clinical study site(s) inspections(s) needed?**
  - **☒ YES ☐ NO**
  
  **If no, explain:**

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| **Advisory Committee Meeting needed?** | ☒ YES |
| **Comments:** |  |
| If no, for an NME NDA or original BLA, include the reason. For example: |  |
| o this drug/biologic is not the first in its class |  |
| o the clinical study design was acceptable |  |
| o the application did not raise significant safety or efficacy issues |  |
| o the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease |  |
| Date if known: |  |
| ☐ NO |  |
| ☐ To be determined |  |
| Reason: |  |

| **If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?** | ☒ Not Applicable |
| **Comments:** |  |

| **CONTROLLED SUBSTANCE STAFF** | ☒ Not Applicable |
| **Abuse Liability/Potential** |  |
| **Comments:** |  |
| ☐ Review issues for 74-day letter |  |

| **CLINICAL MICROBIOLOGY** | ☒ Not Applicable |
| **Comments:** |  |
| ☐ Review issues for 74-day letter |  |

| **CLINICAL PHARMACOLOGY** | ☒ Not Applicable |
| **Comments:** |  |
| ☐ Review issues for 74-day letter |  |

<p>| <strong>Clinical pharmacology study site(s) inspections(s) needed?</strong> | ☐ YES |
| <strong>BIOSTATISTICS</strong> | ☐ Not Applicable |
| ☒ FILE |  |
| ☐ REFUSE TO FILE |  |</p>
<table>
<thead>
<tr>
<th>Comments:</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Review issues for 74-day letter</td>
<td></td>
</tr>
<tr>
<td><strong>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</strong></td>
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<tr>
<td>Comments:</td>
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</tr>
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<td>Not Applicable</td>
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<tr>
<td>FILE</td>
<td></td>
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<tr>
<td>REFUSE TO FILE</td>
<td></td>
</tr>
<tr>
<td>Review issues for 74-day letter</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOGENICITY (protein/peptide products only)</strong></td>
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<tr>
<td>Comments:</td>
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<tr>
<td>Not Applicable</td>
<td></td>
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<tr>
<td>FILE</td>
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<tr>
<td>REFUSE TO FILE</td>
<td></td>
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<tr>
<td>Review issues for 74-day letter</td>
<td></td>
</tr>
<tr>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
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<tr>
<td>Comments:</td>
<td></td>
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<tr>
<td>Not Applicable</td>
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<tr>
<td>FILE</td>
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<tr>
<td>REFUSE TO FILE</td>
<td></td>
</tr>
<tr>
<td>Review issues for 74-day letter</td>
<td></td>
</tr>
<tr>
<td><strong>New Molecular Entity (NDAs only)</strong></td>
<td></td>
</tr>
<tr>
<td>• Is the product an NME?</td>
<td>YES</td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental Assessment</strong></td>
<td></td>
</tr>
<tr>
<td>• Categorical exclusion for environmental assessment (EA) requested?</td>
<td></td>
</tr>
<tr>
<td>If no, was a complete EA submitted?</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
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<tr>
<td>If EA submitted, consulted to EA officer (OPS)?</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td><strong>Quality Microbiology</strong></td>
<td></td>
</tr>
<tr>
<td>• Was the Microbiology Team consulted for validation of sterilization?</td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
</tr>
<tr>
<td>Not Applicable</td>
<td></td>
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<tr>
<td>Facility Inspection</td>
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<td>------------------------------------</td>
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<tr>
<td>Establishment(s) ready for inspection?</td>
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<tr>
<td>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</td>
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<td>Comments: <em>new system in OPQ, EES no longer used</em></td>
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<tr>
<td>Facility/Microbiology Review (BLAs only)</td>
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<tr>
<td>Comments:</td>
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<td></td>
<td></td>
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<tr>
<td>CMC Labeling Review</td>
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<td>Comments:</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</td>
<td></td>
</tr>
<tr>
<td>Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</td>
<td></td>
</tr>
<tr>
<td>If so, were the late submission components all submitted within 30 days?</td>
<td></td>
</tr>
<tr>
<td>What late submission components, if any, arrived after 30 days?</td>
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</tr>
<tr>
<td>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>YES</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</td>
<td></td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</td>
<td></td>
</tr>
</tbody>
</table>

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Sharon Hertz, MD

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): May 19, 2015

**21st Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

- [ ] The application is unsuitable for filing. Explain why:
- [x] The application, on its face, appears to be suitable for filing.

**Review Issues:**

- [ ] No review issues have been identified for the 74-day letter.
- [x] Review issues have been identified for the 74-day letter.

**Review Classification:**

- [x] Standard Review
- [ ] Priority Review

**ACTIONS ITEMS**

- [ ] Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
- [ ] If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
- [ ] If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- [ ] 351(k) BLA/supplement: If filed, send filing notification letter on day 60

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<table>
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<tr>
<th></th>
<th>If priority review:</th>
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<tbody>
<tr>
<td></td>
<td>• notify sponsor in writing by day 60 (see CST for choices)</td>
</tr>
<tr>
<td></td>
<td>• notify OMPQ (so facility inspections can be scheduled earlier)</td>
</tr>
<tr>
<td>☒</td>
<td>Send review issues/no review issues by day 74</td>
</tr>
<tr>
<td></td>
<td>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</td>
</tr>
<tr>
<td></td>
<td>Update the PDUFA V DARRTS page (for applications in the Program)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
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</table>

Annual review of template by OND ADRAs completed: September 2014
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
02/11/2015

PARINDA JANI
02/11/2015
CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 208-090  
Applicant: Collegium Pharm.  
Filing Date: February 10, 2015  
Drug Name: Oxycodone DETERx  
IND Number: 75786  
(Oxycodone ER Capsules)

<table>
<thead>
<tr>
<th>Checklist</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Abuse potential assessment is required if any of the following are true for a drug:
| It affects the CNS                                                      | x   |     |    |                                                                                                                                         |
| It is chemically or pharmacologically similar to other drugs with known abuse potential | x   |     |    |                                                                                                                                         |
| It produces psychoactive effects such as sedation, euphoria, and mood changes | x   |     |    |                                                                                                                                         |
| Is the drug a new molecular entity?                                      |     | x  |    |                                                                                                                                         |
| Is this a new or novel drug formulation?                                 |     | x  |    |                                                                                                                                         |

Content of NDA abuse potential section:

Module 1: Administrative Information and Prescribing Information

1.1.4 Multiple Module Information Amendment contains:

- A summary, interpretation, and discussion of abuse potential data provided in the NDA. | x |
- A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential. | x |
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA | x |

Module 2: Summaries

2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential. | x |

Module 3: Quality

3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical | x |

---

1 21 CFR 314.50(d)(vii): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21 USC 811(f): Abuse potential: if, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.
## CSS Filing Checklist for NDA/BLA or Supplement

<table>
<thead>
<tr>
<th>Checklist</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?</td>
<td></td>
<td>x</td>
<td></td>
<td>Category 1 in vitro studies will be reviewed by OPS with results of the AD-related chemistry review provided to CSS at the mid-cycle meeting.</td>
</tr>
<tr>
<td>3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this an extended release or abuse-resistant formulation?</td>
<td></td>
<td>x</td>
<td></td>
<td>Product is extended release and abuse-resistant formulation</td>
</tr>
</tbody>
</table>

### Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

| 4.2.1.1 Primary Pharmacodynamics - contains study reports (in vitro and in vivo) describing the binding profile of the parent drug and all active metabolites. |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

- Are in vitro receptor binding studies included?                                                                                             | x  |
- Are functional assays included?                                                                                                            | x  |

4.2.3.7.4 Dependence – section includes:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all nonclinical abuse potential studies.

### Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA

| Was a self administration study conducted?                                                                                              | x  |
| Was a conditioned place preference study conducted?                                                                                     | x  |
| Was a drug discrimination study conducted?                                                                                              | x  |
| Was a physical dependence study conducted?                                                                                              | x  |

### Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.

### Human abuse potential study:

| Was a human abuse potential study conducted?                                                                                              | x  |

---

Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA

The abuse potential of oxycodone is known, thus animal behavioral studies are not needed.

---

### Module 5: Clinical Study Reports

5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.

### Human abuse potential study:

| Was a human abuse potential study conducted?                                                                                              | x  |

Two HAP studies were conducted. 

1. **Intranasal Study CP-OXYDET-21** was a randomized, double-blind, double-dummy, positive- and placebo-controlled, single dose, 4-way, crossover study to evaluate the abuse potential and PK parameters of crushed 40 mg oxycodone DETERx intranasal, intact 40 mg oxycodone DETERx oral, and crushed 40 mg IR oxycodone intranasal.

2. **Oral Study CP-OXYDET-24** was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6 treatment, 6-period crossover study to evaluate oral abuse potential of intact and chewed Oxycodone DETERx under...
<table>
<thead>
<tr>
<th>Checklist</th>
<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are all the primary data included in the NDA?</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is a Statistics consult necessary?</td>
<td>x</td>
<td></td>
<td></td>
<td>Yes. CSS has provided a request to the Office of Biostatistics for statistical reviews of studies CP-OXYDET-21 and CP-OXYDET-24. See DARRTS, NDA 208090, January 8, 2015.</td>
</tr>
<tr>
<td>Other Clinical trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there evidence of drug accountability issues or overt evidence of</td>
<td>x</td>
<td></td>
<td></td>
<td>Evidence of diversion and abuse were documented in the Phase 3 study CP-OXYDET-08</td>
</tr>
<tr>
<td>misuse, abuse, or diversions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are all abuse/misuse Case Report Forms submitted [addiction, abuse,</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>misuse, overdose, drug diversion/drug accountability, discrepancies in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amount of the clinical supplies of the study drug, noncompliance,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>protocol violations, lack of efficacy, individuals lost to follow-up,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and any other reasons why subjects dropped out of the study]??</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does Compliance need to be consulted re: site inspection for data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>integrity or other issues?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.6.1 Reports of Postmarketing Experience - includes information to all</td>
<td>x</td>
<td></td>
<td></td>
<td>Oxycodone DETERx has not previously been marketed in the U.S. or in other countries.</td>
</tr>
<tr>
<td>postmarketing experience with abuse, misuse, overdose, and diversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>related to this product</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you review the scientific literature?</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you conducted a search of databases and other information related</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to misuse, abuse, and addiction?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there evidence for any of the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental overdose in the patient population and vulnerable populations</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overdose associated with misuse and abuse</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintended pediatric exposures to product</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labeling issues</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug disposal issues?</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmarketing activities [PMRs, PMCs, REMS]</td>
<td>x</td>
<td></td>
<td></td>
<td>REMS</td>
</tr>
<tr>
<td>Scheduling activities</td>
<td></td>
<td></td>
<td></td>
<td>According to Sponsor, Oxycodone DETERx is in Schedule II of the CSA due to the presence of oxycodone (a Schedule II substance).</td>
</tr>
</tbody>
</table>
CSS Filing Checklist for NDA/BLA or Supplement

Is NDA FILEABLE from a CSS perspective? _______________________________ Yes _______________________________

If the Application is not fileable, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CSS Reviewer: James M. Tolliver, Ph.D. Date: February 6, 2015

Team Leader: Silvia Calderon, Ph.D. Date: February 6, 2015
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES M TOLLIVER
02/06/2015

SILVIA N CALDERON
02/06/2015

MICHAEL KLEIN
02/10/2015
REGULATORY PROJECT MANAGER
PHYSICIAN’S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208090

Application Type: New NDA

Name of Drug/Dosage Form: Xtampza (oxycodone extended-release) capsules

Applicant: Collegium Pharmaceuticals, Inc.

Receipt Date: December 12, 2014

Goal Date: October 12, 2015

1. Regulatory History and Applicant’s Main Proposals
The sponsor submitted a 505b2 NDA submission for an abuse deterrent, extended-release oxycodone product for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. The sponsor is referencing the agency’s previous finding of efficacy and safety for OxyContin®

2. Review of the Prescribing Information
This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3. Conclusions/Recommendations
SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Submit revised labeling in portrait page orientation not landscape.
2. Submit the medication guide as part of labeling

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 25, 2015. The resubmitted PI will be used for further labeling review.
Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 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.
   Comment: Set margins so that they are .5 inches

NO 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.
   Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
   Comment:

NO 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.
   Comment: The headings should be in the center of a solid horizontal line not a dashed line.

NO 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.
   Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
   Comment:

NO 7. Section headings must be presented in the following order in HL:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>• Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>• Initial U.S. Approval</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

- Boxed Warning: Required if a BOXED WARNING is in the FPI
- Recent Major Changes: Required for only certain changes to PI*
- Indications and Usage: Required
- Dosage and Administration: Required
- Dosage Forms and Strengths: Required
- Contraindications: Required (if no contraindications must state “None.”)
- Warnings and Precautions: Not required by regulation, but should be present
- Adverse Reactions: Required
- Drug Interactions: Optional
- Use in Specific Populations: Optional
- Patient Counseling Information Statement: Required
- Revision Date: Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: Your label does not include a Revision Date

HIGHLIGHTS DETAILS

Highlights Heading

NO 8. At the beginning of HL, the following heading must be bolded and should appear in all UPPER CASE letters: “HIGHLIGHTS OF PRESCRIBING INFORMATION”.

Comment: This statement is not bolded

Highlights Limitation Statement

NO 9. 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.

Comment: This statement is not bolded and does not contain the proposed proprietary name.

Product Title in Highlights

NO 10. Product title must be bolded.

Comment: The product title is not bolded

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be bolded.

Comment:

YES 13. The BW 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”). The BW heading should be centered.
Selected Requirements of Prescribing Information

Comment: The text is not in a box

YES 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement should be centered immediately beneath the heading and appear in italics.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “See full prescribing information for complete boxed warning.”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

N/A 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES
21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

NO 22. 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”.

Comment: Insert a valid contact number

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product does not have FDA-approved patient labeling:

- “See 17 for PATIENT COUNSELING INFORMATION”

If a product has FDA-approved patient labeling:

- “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment: Bold the entire statement

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 9/2013”).

Comment:
Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPER CASE letters and bolded.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and bolded.

Comment:

YES 28. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

NO 31. 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.”

Comment: Omit Section 15 References, if there aren't any references include in the FPI
### Full Prescribing Information (FPI)

**FULL PRESCRIBING INFORMATION: GENERAL FORMAT**

<table>
<thead>
<tr>
<th>1</th>
<th>INDICATIONS AND USAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3</td>
<td>DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4</td>
<td>CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5</td>
<td>WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6</td>
<td>ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7</td>
<td>DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8</td>
<td>USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>8.2</td>
<td>Labor and Delivery</td>
</tr>
<tr>
<td>8.3</td>
<td>Nursing Mothers</td>
</tr>
<tr>
<td>8.4</td>
<td>Pediatric Use</td>
</tr>
<tr>
<td>8.5</td>
<td>Geriatric Use</td>
</tr>
<tr>
<td>9</td>
<td>DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1</td>
<td>Controlled Substance</td>
</tr>
<tr>
<td>9.2</td>
<td>Abuse</td>
</tr>
<tr>
<td>9.3</td>
<td>Dependence</td>
</tr>
<tr>
<td>10</td>
<td>OVERDOSAGE</td>
</tr>
<tr>
<td>11</td>
<td>DESCRIPTION</td>
</tr>
<tr>
<td>12</td>
<td>CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1</td>
<td>Mechanism of Action</td>
</tr>
<tr>
<td>12.2</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>12.3</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>12.4</td>
<td>Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5</td>
<td>Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13</td>
<td>NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1</td>
<td>Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2</td>
<td>Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14</td>
<td>CLINICAL STUDIES</td>
</tr>
<tr>
<td>15</td>
<td>REFERENCES</td>
</tr>
<tr>
<td>16</td>
<td>HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17</td>
<td>PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “*[see Warnings and Precautions (5.2)]*” or “*[see Warnings and Precautions (5.2)]*”.

**Comment:** The cross-reference numbers should be in 12 pt font size.
34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

**NO** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

**Comment:**

BOXED WARNING Section in the FPI

**NO** 36. In the BW, all text should be **bolded**.

**Comment:** Include the boxed warning in the FPI.

**NO** 37. The BW 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**”).

**Comment:**

CONTRAINDICATIONS Section in the FPI

**YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

ADVERSE REACTIONS Section in the FPI

**YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> “The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

PATIENT COUNSELING INFORMATION Section in the FPI

**YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and
Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

NO 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: Attach the Medication Guide at the end of the PI.
Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

RECENT MAJOR CHANGES
[section (X,X)]
[section (X,X)]

INDICATIONS AND USAGE
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSEAGE AND ADMINISTRATION
• [text]
• [text]

DOSEAGE FORMS AND STRENGTHS
[text]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 WARNING: [SUBJECT OF WARNING]
1.1 INDICATIONS AND USAGE
1.1.1 [text]
1.1.2 [text]

1.2 DOSEAGE AND ADMINISTRATION
1.2.1 [text]
1.2.2 [text]

1.3 DOSEAGE FORMS AND STRENGTHS
1.3.1 [text]

1.4 CONTRAINDICATIONS
1.4.1 [text]

1.5 WARNINGS AND PRECAUTIONS
1.5.1 [text]

1.6 ADVERSE REACTIONS
1.6.1 [text]

1.7 DRUG INTERACTIONS
1.7.1 [text]

1.8 USE IN SPECIFIC POPULATIONS
1.8.1 Pregnancy
1.8.2 Labor and Delivery
1.8.3 Nursing Mothers
1.8.4 Pediatric Use
1.8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence

10 OVERDOSAGE

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
14.1 [text]

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Full text content is not visible due to the withheld pages.
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
01/21/2015