

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**207621Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

| <b>Application Information</b>  |  |                              |
|---|--|------------------------------|
| NDA # 207621  | NDA Supplement #: S-                             | Efficacy Supplement Type SE- |
| Proprietary Name: Troxyca ER<br>Established/Proper Name: ALO-02 (Oxycodone hydrochloride and naltrexone hydrochloride)<br>Dosage Form: Extended –release Capsule<br>Strengths: 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg |  |                              |
| Applicant: Pfizer, Inc<br>Agent for Applicant (if applicable): N/A  |  |                              |
| Date of Application: December 19, 2014<br>Date of Receipt: December 19, 2014  |  |                              |
| PDUFA Goal Date: October 19, 2015 originally, then January 19, 2016 for the Major Amendment 3-month extension.  | Action Goal Date (if different): August 19, 2016 |                              |
| RPM: Diana Walker   |  |                              |
| Proposed Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.   |  |                              |

**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.)*

| Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph) | Information relied-upon (e.g., specific sections of the application or labeling)  |
|---|---|
| Oxycodone (Roxicodone®, NDA 021011)   | Label: indication, and Sections 2, 4, 5, 7, 9, 8, 9, 10, 12, 13<br>Agency's previous findings of safety and effectiveness   |
| Naltrexone HCl (Revia®, NDA 018932)   | Label: indication, and Sections 4, 8, 12<br>Agency's previous findings of safety and effectiveness  |
| Published literature  | Nonclinical safety justification for excipients   |
| Morphine sulfate and naltrexone HCl (Embeda; NDA 22321)   | In addition, the Applicant will rely on data generated from EMBEDA studies <span style="background-color: gray; color: gray;">(b) (4)</span><br><br>The Applicant also listed Embeda in their annotated draft labeling. However, these annotations do not represent any specific information from Embeda. Rather they represent examples of a recent version of class-labeling. |

\*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<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

**Study B4531007 established the extent of bioavailability (BA) of oxycodone from the to-be-marketed pellet formulation of ALO-02 compared to IR oxycodone (Roxicodone IR Tablets).**

**The scientific justification supporting the bridge to the Agency's findings of safety and effectiveness for Revia consisted of: (1) a comparison of the relative amount of**

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

naltrexone in Troxyca ER compared to 50 mg of naltrexone in Revia (i.e., the lowest strength); and (2) the fact that the naltrexone in Troxyca ER is sequestered resulting in systemic exposure below the limit of detection compared to the higher systemic exposure of naltrexone from Revia, as reflected in the published literature for 50 mg Revia. A relative bioavailability study comparing Troxyca ER and Revia to support the bridge was not conducted (or expected by FDA) because of safety concerns associated with possible study designs.

The bridge to the nonclinical data (published literature; Embeda) is based on a scientific explanation (i.e., the studies employed the same molecule). In other words, the published literature included studies that tested the exact same molecule as the molecule under review; therefore, the division concluded that the data were relevant to the question at hand.

#### 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

<sup>1</sup>For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 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):

| Name of Listed Drug              | NDA #      | Did applicant specify reliance on the product? (Y/N)          |
|----------------------------------|------------|---|
| Oxycodone (Roxicodone®)          | NDA 021011 | Y   |
| Naltrexone HCl (Revia®)          | NDA 018932 | Y   |
| Embeda (morphine and naltrexone) | NDA 22321  | Y (cross-reference as this NDA is also held by the Applicant) |

*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:

**NDA 021011, Roxicodone relied on Percodan.**

**NDA 022321, Embeda relied on Revia (NDA18932)**

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO   
If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- 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").

**The drug product in this application is a combination of the two active ingredients that are separately contained in the products that are relied upon.**

*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)?

N/A  YES  NO

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):

**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):

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)(ii): No relevant patents.
- 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):
- (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):

*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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
08/19/2016

## 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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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: | Final Protocol Submission:                               | 11/2015 |
|                          | Interim Report (Cumulative Enrollment of 470 patients)   | 5/2017  |
|                          | Interim Report (Cumulative Enrollment of 1,042 patients) | 9/2017  |
|                          | Interim Report (Cumulative Enrollment of 1,609 patients) | 1/2018  |
|                          | Interim Report (Cumulative Enrollment of 2,300 patients) | 6/2018  |
|                          | Study Completion:  | 10/2019 |
|                          | Final Report Submission:                                 | 3/2020  |

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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 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.

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)

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

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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)

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- Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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

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 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.

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 #                    | NDA 207621  |                |
| Product Name:            | TROXYCA ER (oxycodone HCl/ naltrexone HCl) 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:  | <u>04/2015</u> |
|                          | Study Completion:   | <u>10/2015</u> |
|                          | Final Report Submission:  | <u>01/2016</u> |

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
- 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 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.

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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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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
- 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 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

- 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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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..

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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
- 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 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

- 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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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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
- 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
- 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 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

- 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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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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
- 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)**

- 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 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

- 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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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PMR Schedule Milestones:

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

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
- 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 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.

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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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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
- 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 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

- 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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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PMR Schedule Milestones:

|                            |                |
|----------------------------|----------------|
| Final Protocol Submission: | <u>03/2015</u> |
| Study Completion:          | <u>03/2017</u> |
| Final Report Submission:   | <u>06/2017</u> |

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 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)

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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)

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Other

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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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.

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PMR Schedule Milestones: Final Protocol Submission: 11/2014  
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
- 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.

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
- 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)

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

Immunogenicity as a marker of safety

Other (provide explanation)

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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

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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 # NDA 207621  
Product Name: TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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PMR Description: 2965-2 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2965-3, conduct a descriptive study that analyzes data on the following:

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

AND

(2) abuse of TROXYCA ER (oxycodone and naltrexone) and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TROXYCA ER (oxycodone and naltrexone) 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.

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|                          |                            |         |
|--------------------------|----------------------------|---------|
| PMR Schedule Milestones: | Final Protocol Submission: | 04/2017 |
|                          | Study Completion:          | 04/2018 |
|                          | Final Report Submission:   | 10/2018 |
|                          | Other:                     | N/A     |

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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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of TROXYCA ER actually deter abuse of the product in “real world” use.

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 TROXYCA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of TROXYCA 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 Troxyca 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 #                      NDA 207621  
Product Name:                 TROXYCA ER (oxycodone HCl/ naltrexone HCl) extended-release capsules

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PMR Description:            2965-3:    Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TROXYCA ER (oxycodone and naltrexone) 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 TROXYCA ER (oxycodone and naltrexone) 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*.

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|                          |                            |                |
|--------------------------|----------------------------|----------------|
| PMR Schedule Milestones: | Final Protocol Submission: | <u>04/2019</u> |
|                          | Study Completion:          | <u>04/2021</u> |
|                          | Final Report Submission:   | <u>10/2021</u> |
|                          | Other:                     | <u>N/A</u>     |

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 TROXYCA 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 TROXYCA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of TROXYCA 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  
 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.

The design of the hypothesis-testing studies for TROXYCA ER will be informed by the patterns of use and the patterns of misuse/ abuse documented in PMR 2965-2. 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 TROXYCA ER. In particular, post-marketing studies for TROXYCA 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.*

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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 # NDA 207621  
Product Name: Troxyca ER (oxycodone and naltrexone) Capsules

---

PMR/PMC Description: 2965-4 Conduct an in vivo comet assay for (b) (4)

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|                              |                            |                   |
|------------------------------|----------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>08/2016</u>    |
|                              | Study/Trial Completion:    | <u>11/2016</u>    |
|                              | Final Report Submission:   | <u>02/2017</u>    |
|                              | Other: _____               | <u>MM/DD/YYYY</u> |

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

This drug substance impurity/drug product degradant has been in naltrexone drug substances and is likely present in other FDA-approved naltrexone containing products. Up until now, no genetic toxicology studies have been completed for this impurity as levels were below the ICH qualification threshold, and the compound was not flagged as a structural alert. The Applicant wished to have drug product specifications above the ICH qualification threshold; therefore, they conducted the required studies. The compound tested negative in the in vitro Ames assay and the in vivo micronucleus assay; however, it tested positive in the in vitro chromosomal aberration assay. As per ICH S2(R1), a fourth study, preferably an in vivo study, should be completed to clarify the positive in vitro finding.

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.”

Genotoxic compounds could ultimately result in damage to the genetic material of cells. This could result in carcinogenicity.

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 an in vivo animal study to characterize the potential genotoxicity of a compound.

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)

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

Immunogenicity as a marker of safety

Other (provide explanation)

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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

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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

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**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.

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NDA # NDA 207621  
Product Name: Troxyca ER (oxycodone and naltrexone) Capsules

---

PMR/PMC Description: 2965-5 Conduct an in vivo comet assay for (b) (4)

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|                              |                            |            |
|------------------------------|----------------------------|------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | 08/2016    |
|                              | Study/Trial Completion:    | 11/2016    |
|                              | Final Report Submission:   | 02/2017    |
|                              | 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

This drug substance impurity/drug product degradant has been in naltrexone drug substances and is likely present in other FDA-approved naltrexone containing products. Up until now, no genetic toxicology studies have been completed for this impurity as levels were below the ICH qualification threshold, and the compound was not flagged as a structural alert. The Applicant wished to have drug product specifications above the ICH qualification threshold; therefore, they conducted the required studies. The compound tested negative in the in vitro Ames assay and the in vivo micronucleus assay; however, it tested positive in the in vitro chromosomal aberration assay. As per ICH S2(R1), a fourth study, preferably an in vivo study, should be completed to clarify the positive in vitro finding.

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.”

Genotoxic compounds could ultimately result in damage to the genetic material of cells. This could result in carcinogenicity.

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 an in vivo animal study to characterize the potential genotoxicity of a compound.

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

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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

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**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.

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NDA # NDA 207621  
Product Name: Troxyca ER (oxycodone and naltrexone) Capsules

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PMR/PMC Description: 2965-6 Conduct a pre- and post-natal development toxicology study in the rat model to assess the potential impact of dibutyl sebacate on development.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 09/2016  
Study/Trial Completion: 03/2017  
Final Report Submission: 11/2017  
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

Dibutyl sebacate has been used in FDA-approved oral drug products but is considered a new excipient based on the maximum theoretical daily dose of this excipient via this drug product formulation. An older suboptimal published study failed to clearly define a no adverse effect level (NOAEL); however, the study employed only a single very high dose of the compound. Given the prior clinical experience and the fact that most individuals will not exceed the levels currently present in previous drug products, the definitive study has been considered acceptable to be completed post-marketing.

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 pre- and postnatal development study assesses the impact of a compound 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. Based on the published older study, there is a potential for decreased body weight of the mother and adverse impact on pup growth and development at high doses.

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 pre- and post-natal developmental toxicology 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)
- 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

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**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)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
08/19/2016

JUDITH A RACOOSIN  
08/19/2016

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**TO:** Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER capsules (new drug application (NDA) 207621)

**FROM:** Emily Helms Williams *KAR for EHW*  
Regulatory Counsel *8/19/16*  
Office of Regulatory Policy (ORP)

Joshua M. Lloyd, MD  
Clinical Team Leader  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**THROUGH:** Carol Bennett *CB 8/19/16*  
Deputy Director, ORP

Sharon Hertz, MD  
Division Director, DAAAP

**DATE:** August 19, 2016

**RE:** Citizen Petition from Purdue Pharma L.P. (FDA-2015-P-5108)

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A citizen petition was submitted on behalf of Purdue Pharma L.P. (Purdue), dated and received on December 22, 2015 (Petition). That Petition was subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires FDA to take final Agency action within 150 days of submission. On May 20, 2016, FDA denied the Petition without comment on the Petition's specific requests, because Pfizer Inc.'s (Pfizer) 505(b)(2) application for ALO-02 (Troxyca ER; oxycodone hydrochloride and naltrexone hydrochloride), which is the subject of the Petition, was pending before the Agency and DAAAP's review was not complete. DAAAP is now completing its review of Pfizer's Troxyca application (NDA 207621). ORP, DAAAP, and other components of the Agency have considered the issues raised in the Petition as they relate to the application. This memorandum documents consideration of the issues.

In the Petition, Purdue states that Pfizer, Inc. (Pfizer) submitted a new drug application (NDA) under section 505(b)(2) of the FD&C Act (21 U.S.C. 355(b)(2)) for ALO-02,<sup>1</sup> a "twice-a-day

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<sup>1</sup> The Petition refers to the drug product at issue as "ALO-02." As discussed further below, the proprietary name for the product referred to in the Petition is Troxyca ER. We use the proprietary name for the drug product in this memorandum except when discussing the Petition's requests or quoting from the Petition.

solid oral dosage form of oxycodone intended to impede abuse and misuse.” Petition at 1. The Petition requests that the Food and Drug Administration (FDA or Agency):

- (1) Require that Pfizer’s 505(b)(2) NDA for ALO-02 be withdrawn and resubmitted with (i) correct references to the listed drugs OxyContin (oxycodone hydrochloride (HCl) controlled-release) tablets (NDA 022272) and Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets) (NDA 205777), and (ii) appropriate certifications with respect to all patents listed in Approved Drug Products With Therapeutic Equivalence Evaluations (the Orange Book) for those NDAs, as required under 21 U.S.C. 355(b)(4)(A); and
- (2) Refuse to approve Pfizer’s NDA until such time as (i) Pfizer includes in its application an appropriate certification with respect to all patents listed in the Orange Book for OxyContin (NDA 022272) and Targiniq ER (NDA 205777), and (ii) if Pfizer certifies that any of these patents is invalid, unenforceable, or will not be infringed by the manufacture, marketing, and distribution of ALO-02, Pfizer complies with the notice provisions of 21 U.S.C. 355(b)(3).

Petition at 3. We have carefully reviewed the Petition, its exhibits, and other information available to the Agency as they relate to this application.<sup>2</sup>

## **I. BACKGROUND**

Below we provide background on products that Purdue asserts must be relied on by Pfizer for approval of its 505(b)(2) NDA for ALO-02 (OxyContin and Targiniq ER), followed by background on Pfizer’s ALO-02 and products relied on or cross-referenced by Pfizer for approval (Roxicodone, Revia, and Embeda).

### **A. Original and Reformulated OxyContin**

In December 1995, the Agency approved NDA 020553 for OxyContin (oxycodone HCl controlled-release tablets) in dosage strengths of 10, 20, and 40 milligrams (mg), which was submitted under section 505(b)(1) of the FD&C Act (a stand-alone NDA). NDA 020553 is held by Purdue.

OxyContin was the first extended-release oxycodone product approved by the Agency. FDA subsequently approved additional dosage strengths of OxyContin (hereafter jointly referred to as Original OxyContin). Original OxyContin was labeled for administration every 12 hours. It was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. Original OxyContin also was manipulated for therapeutic purposes, for example, by crushing the product to sprinkle it onto food or to administer it through a gastric tube. As noted in the boxed warning of the labeling for Original

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<sup>2</sup> As noted in the Petition, Purdue had previously submitted a citizen petition dated June 9, 2015 (Docket No. FDA-2015-P-2120), requesting that FDA take the same actions. We denied that Petition on November 6, 2015, without comment on whether we would take the actions requested.

OxyContin, disruption of the tablet and controlled-release mechanism for abuse or misuse ““ can lead to rapid release and absorption of a potentially fatal dose of oxycodone.”” 78 FR 23273 (April 18, 2013) (quoting the Original OxyContin labeling).

Purdue reformulated the product with physicochemical properties intended to make the tablet more difficult to manipulate for purposes of abuse or misuse and submitted a new application for oxycodone HCl controlled-release tablets (NDA 022272) in November 2007. In April 2010, the Agency approved Reformulated OxyContin, which was submitted under section 505(b)(1) of the FD&C Act, with dosage strengths of 10, 15, 20, 30, 40, 60, and 80 mg (hereafter referred to as Reformulated OxyContin). Reformulated OxyContin 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. Several patents for Reformulated OxyContin are listed in the Orange Book.

In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of Original OxyContin, and FDA subsequently moved Original OxyContin to the “Discontinued Drug Product List” (Discontinued) section of the Orange Book. In April 2013, FDA approved a supplemental application for Reformulated OxyContin, approving changes to the product labeling that describe certain abuse-deterrent properties of the reformulated product. Shortly after, FDA announced in a Federal Register notice its determination that Original OxyContin was withdrawn from sale for reasons of safety or effectiveness because, although it had the same therapeutic benefits as Reformulated OxyContin, it posed an increased potential for abuse by certain routes of administration, when compared to Reformulated OxyContin. 78 FR 23273 (April 18, 2013). Therefore, based on the totality of the data and information available to the Agency at the time, FDA concluded that the benefits of Original OxyContin no longer outweighed its risks. 78 FR 23274. In that Federal Register notice, FDA also stated that the Agency will remove Original OxyContin from the list of products published in the Orange Book, and it subsequently did so. 78 FR 23275. Purdue voluntarily requested that approval of the application for Original OxyContin be withdrawn and waived its opportunity for a hearing. FDA withdrew approval of the application under section 505(e) of the FD&C Act in August 2013. 78 FR 48177 (Aug. 7, 2013).

## **B. Targiniq ER**

In July 2014, the Agency approved NDA 205777 for Targiniq ER (oxycodone HCl and naloxone HCl extended-release tablets) in dosage strengths of 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg, which was submitted under the pathway described in section 505(b)(2) of the FD&C Act (a 505(b)(2) NDA). Purdue holds NDA 205777. The Targiniq ER NDA cited Narcan (naloxone hydrochloride; NDA 16636) as the listed drug<sup>3</sup> relied upon and cross-referenced Purdue’s NDAs for Original OxyContin and Reformulated OxyContin. Targiniq ER 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. Targiniq ER has pharmacologic properties that are expected to reduce abuse by the intranasal and intravenous

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<sup>3</sup> See 21 CFR 314.3 (defining listed drug).

routes of administration. Targiniq ER has not been marketed and is listed in the Discontinued section of the Orange Book. Several patents for Targiniq ER are listed in the Orange Book.

### **C. ALO-02/Troxyca ER**

In December 2014, Pfizer submitted a 505(b)(2) NDA (207621) for ALO-02 (oxycodone HCl and naltrexone HCl extended-release capsules) (hereafter referred to as Troxyca ER). Troxyca ER includes dosages of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg. Troxyca ER is taken twice daily and 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.” The Troxyca ER NDA cited Roxicodone (NDA 021011) (oxycodone HCl tablets USP) and Revia (NDA 18932) (naltrexone hydrochloride) as the listed drugs relied upon. Pfizer’s application also cross-references its own NDA 022321 for Embeda (morphine sulfate and naltrexone HCl). The Agency approved Pfizer’s Troxyca ER NDA today.

### **D. Roxicodone**

In August 2000, the Agency approved a 505(b)(2) NDA (021011) for Roxicodone (oxycodone HCl tablets USP). Mallinckrodt Inc. (Mallinckrodt) holds NDA 021011. Roxicodone is available in 5, 15, and 30 mg dosage strengths and is designed to provide immediate-release of oxycodone. The Roxicodone NDA cited Percodan (oxycodone hydrochloride and aspirin, NDA 7377) as the listed drug relied upon. Roxicodone is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. There are no patents for Roxicodone listed in the Orange Book.

### **E. Revia**

In November 1984, the Agency approved NDA 18932 for Revia (naltrexone HCl). Teva Women’s Health, Inc. holds NDA 18932. Revia is an opioid antagonist that blocks, reversibly, the subjective effects of exogenously administered opioids. It is supplied as a tablet and indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. There are no patents for Revia listed in the Orange Book.

### **F. Embeda**

In August 2009, the Agency approved NDA 022321 for Embeda (morphine sulfate and naltrexone HCl) extended-release capsules, which was submitted under the pathway described in section 505(b)(2) of the FD&C Act. It is available in dosage strengths of 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg. The original application holder for Embeda was Alpharma Pharmaceuticals, which was subsequently acquired by Pfizer. The Embeda NDA cited Revia as the listed drug relied upon. Embeda is a fixed-combination drug product that is an extended-release capsule containing morphine sulfate and naltrexone hydrochloride. Embeda 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. It has properties that are expected to reduce abuse by the intranasal and

oral routes of administration. Several patents for Embeda are listed in the Orange Book.

## II. LEGAL FRAMEWORK

### A. 505(b)(2) NDAs

Section 505(b)(2) of the FD&C Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417 (the Hatch-Waxman Amendments). The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low-cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.<sup>4</sup>

Section 505(b)(2) of the FD&C Act describes an application that contains full reports of investigations of safety and effectiveness, where at least some of the information relied upon by the applicant for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., published literature and/or the Agency's finding of safety and/or effectiveness for one or more listed drugs). When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product (i.e., a listed drug), the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can bridge<sup>5</sup> its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability<sup>6</sup> of the two products or other appropriate scientific information. A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug(s). The 505(b)(2) application must include sufficient data to support any differences between the proposed drug and the listed drug(s) and demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness. The 505(b)(2) pathway permits sponsors to rely on what is already known about a drug, thereby avoiding unnecessary duplication of human or animal studies and conserving resources.

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<sup>4</sup> See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

<sup>5</sup> A *bridge* in a 505(b)(2) NDA is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA. See also FDA draft guidance for industry Applications Covered by Section 505(b)(2) (Draft 505(b)(2) Guidance) at 8-9, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. We update guidances periodically. The most recent versions of guidances are available on the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>6</sup> Bioavailability data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's guidance for industry entitled "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations," at 3.

A sponsor interested in submitting a 505(b)(2) NDA that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs<sup>7</sup> should determine which listed drug(s) is most appropriate for its development program, and must establish that such reliance is scientifically appropriate.<sup>8</sup> However, if there is a listed drug that is a "pharmaceutical equivalent"<sup>9</sup> to the proposed drug product, FDA advises that a sponsor should identify the pharmaceutically equivalent product as a listed drug and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.<sup>10</sup> This approach is intended to prevent applicants from using the 505(b)(2) pathway to avoid patent protections that would have applied had an abbreviated new drug application (ANDA) been submitted under section 505(j).<sup>11</sup>

## B. Patents

A 505(b)(2) applicant is required to submit an appropriate patent certification or statement with respect to each patent which claims the drug(s) relied on for approval or which claim a method of using the drug(s) for which the applicant is seeking approval and for which information is required to be submitted under section 505(b)(1) or 505(c)(2) of the FD&C Act (see section 505(b)(2)(A)-(B) of the FD&C Act).

Section 505(b)(1) of the FD&C Act requires NDA applicants to submit as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).<sup>12</sup>

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<sup>7</sup> For example, in certain cases, a sponsor may rely on FDA's finding of safety and/or effectiveness for different listed drugs to support different aspects of its development program (e.g., where appropriate, reliance on oral and topical dosage forms containing the same active ingredient to support systemic and local toxicology, respectively).

<sup>8</sup> See FDA Response to Sanzo, Chasnow, Lawton, and Rakoczy (October 14, 2003) (Joint 505(b)(2) Petition Response) at 12. This joint response was previously assigned Docket Nos. 2001P-0323, 2002P-0047, and 2003P-0408, but as a result of FDA's transition to its new docketing system (Regulations.gov) these numbers were combined to Docket No. FDA-2003-P-0274.

<sup>9</sup> *Pharmaceutical equivalents* are drug products with:

. . . identical dosage forms that 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 . . . that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients, and meet the identical compendial or other applicable standards of identity, strength, quality and purity, including potency, and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

21 CFR 320.1(c).

<sup>10</sup> FDA draft 505(b)(2) guidance.

<sup>11</sup> The Agency may refuse to file a 505(b)(2) NDA for a drug that is a duplicate of a listed drug and is eligible for approval as an ANDA under section 505(j) of the FD&C Act (21 CFR 314.101(d)(9)).

<sup>12</sup> Section 505(c)(2) of the FD&C Act imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

FDA is required to publish the patent information provided by the NDA holder for drugs approved under 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act, and 21 CFR 314.53(e)).

For each unexpired patent listed in the Orange Book for a listed drug it references, the 505(b)(2) applicant must submit either a paragraph III certification (delaying approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the applicant is seeking approval and for which information is required to be filed under section 505(b) and (c) of the FD&C Act (section 505(b)(2)(A) and (B) of the FD&C Act).<sup>13, 14</sup> The applicant is not required to certify to all patents “for every drug containing the same active ingredient that relied in part on the same underlying investigations on which the 505(b)(2) applicant seeks to rely.”<sup>15</sup> Rather, the applicant’s patent certification obligations are limited to those patents that claim the *specific listed drug* upon which the applicant has relied for FDA’s finding of safety and effectiveness to support the approval of the 505(b)(2) NDA.<sup>16</sup>

A 505(b)(2) applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder for the listed drug(s) and each patent owner with notice of its patent certification, including a description of the legal and factual basis for its assertion that the patent is invalid or will not be infringed (section 505(b)(3) of the FD&C Act).<sup>17</sup> Should the NDA holder or patent owner initiate a patent infringement action against the 505(b)(2) applicant within 45 days of receiving the required notice, approval of the 505(b)(2) NDA generally will be stayed for 30 months from the date of receipt of the notice, unless a court orders otherwise (section 505(c)(3)(C) of the FD&C Act).<sup>18</sup> This process may permit resolution of patent infringement issues before the product described in the 505(b)(2) NDA is approved and marketed.

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<sup>13</sup> A 505(b)(2) applicant may also submit a paragraph I certification (that such patent information has not been filed) or paragraph II certification (that such patent has expired).

<sup>14</sup> See also, e.g., 21 CFR 314.50(i)(1) and 21 CFR 314.53 (FDA regulations implementing patent listing and certification provisions).

<sup>15</sup> FDA Response to Abbott Laboratories and Laboratoires Fournier (November 30, 2004) (Docket No. FDA-2004-P-0089) (previously Docket No. 2004P-0386) (Fenofibrate Petition Response) at 6 (emphasis added).

<sup>16</sup> See *Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell*, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015) (holding that the applicant need only certify to the product patents or the method-of-use patents that are associated with the reference listed drug (i.e., the drug product on whose finding of safety or effectiveness the 505(b)(2) applicant relies)), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

<sup>17</sup> See e.g., 21 CFR 314.52.

<sup>18</sup> See e.g., 21 CFR 314.107.

### III. DISCUSSION

#### A. Pfizer's Troxyca ER is Safe and Effective and Otherwise Meets the Standards for Approval

Pfizer's 505(b)(2) NDA for Troxyca ER includes the data and information necessary to establish the safety and effectiveness of the drug product proposed in the application. As stated above, Troxyca ER relies upon the Agency's previous findings of safety and effectiveness for Roxycodone (oxycodone HCl tablets USP) and Revia (naltrexone HCl).<sup>19</sup> Pfizer's 505(b)(2) NDA includes data from relative bioavailability studies to bridge to the Agency's findings of safety and effectiveness for Roxycodone (for the oxycodone component) and a scientific justification to bridge to Revia (for the naltrexone component).<sup>20</sup> In addition, Pfizer's 505(b)(2) NDA includes, among other things: data from two Phase 3 clinical trials (one randomized, placebo-controlled study and one long-term, open-label study) to confirm the effectiveness and safety of the extended-release formulation of the drug product when dosed twice daily; a cross-reference to Pfizer's own 505(b)(2) NDA for Embeda (morphine sulfate and naltrexone HCl) to support the qualification of naltrexone impurities and degradants in the Troxyca ER formulation;<sup>21</sup> published literature, and in vitro and in vivo studies to evaluate the abuse-deterrent properties of the formulation.

The studies submitted by Pfizer, as well as the Agency's findings of safety and/or effectiveness for Roxycodone and Revia, the cross-reference to Pfizer's 505(b)(2) NDA for Embeda, and published literature were relied on for approval and support the Agency's finding that Troxyca ER is a safe and effective drug product. FDA did not rely on data from or the finding of safety and effectiveness for other drugs for approval of Pfizer's 505(b)(2) NDA for Troxyca ER. To the extent Pfizer mentioned other products in its 505(b)(2) NDA for Troxyca ER (i.e., to the extent it submitted results from an OxyContin arm of a clinical trial, as discussed below), those products and data were neither essential for approval, nor were they relied upon by the Agency to approve the 505(b)(2) NDA for Troxyca ER and to find it safe and effective.

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<sup>19</sup> There is no pharmaceutical equivalent to Troxyca ER listed in the Orange Book. In the absence of a pharmaceutical equivalent, a sponsor can determine which listed drug(s) is most appropriate for its development program as Pfizer did here, as long as the applicant establishes that reliance on the listed drug(s) is scientifically appropriate and submits data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s).

<sup>20</sup> The scientific justification supporting the bridge to the Agency's findings of safety and effectiveness for Revia consisted of: (1) a comparison of the relative amount of naltrexone in Troxyca ER compared to 50 mg of naltrexone in Revia (i.e., the lowest strength); and (2) the fact that the naltrexone in Troxyca ER is sequestered resulting in systemic exposure below the limit of detection compared to the higher systemic exposure of naltrexone from Revia as reflected in the published literature for 50 mg Revia. A relative bioavailability study comparing Troxyca ER and Revia to support the bridge was not conducted by the sponsor (or required by FDA) because of safety concerns associated with possible study designs.

<sup>21</sup> Pfizer's 505(b)(2) NDA for Troxyca ER cross-references its own 505(b)(2) NDA for Embeda, which in turn relies on Revia. Pfizer complied with patent certification provisions, which involved a certification of no relevant patents.

## **B. The Petition Arguments Lack Merit**

In support of its two requests, the Petition raises the following three arguments:

- (1) That Pfizer must reference Reformulated OxyContin in its 505(b)(2) NDA for ALO-02 because a comparative study with OxyContin that Pfizer conducted in 2012 was included by Pfizer in its pending NDA for ALO-02;
- (2) That because Pfizer relies upon the listed drug Roxicodone IR in its 505(b)(2) NDA for ALO-02, the application must reference OxyContin as well; and
- (3) That Pfizer must reference Targiniq ER in its 505(b)(2) NDA for ALO-02 because Targiniq ER is the “most similar listed drug” to ALO-02.

These arguments are addressed in turn below.

### **1. Pfizer’s Study Using Troxyca ER and Reformulated OxyContin**

The Petition states that, in 2012, Pfizer conducted a study comparing the pharmacokinetics (PK), safety, and tolerability of ALO-02 (40 mg twice daily (BID) and 80 mg once daily (QD)) and Reformulated OxyContin (40 mg BID), and that Pfizer acknowledged including the study in its pending NDA. Petition at 10. The Petition cites one published article authored by Pfizer;<sup>22</sup> and states that the published version of the article includes certain comparisons between the ALO-02 arms and Reformulated OxyContin, and that, based on the comparisons with Reformulated OxyContin, the authors conclude that ALO-02 is suitable for administration around the clock to treat chronic pain. Petition at 12. The Petition states that the study’s showing that ALO-02 and Reformulated OxyContin have similar safety and tolerability, and are comparable on relevant PK parameters (despite certain differences) constitutes a “direct bridge” between ALO-02 and the findings of safety and efficacy for Reformulated OxyContin. *Id.* at 12. According to the Petition, because of this direct comparison, Pfizer must reference Reformulated OxyContin in its 505(b)(2) NDA and certify to the patents listed in NDA 022272.

#### *FDA Response*

Pfizer conducted a study using Troxyca ER and Reformulated OxyContin<sup>23</sup> in 2012, and that study was submitted in Pfizer’s 505(b)(2) NDA for Troxyca ER. This study was an open-label, single- and multiple-dose, cross-over, pharmacokinetic study comparing Troxyca ER 40 mg/4.8

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<sup>22</sup> Gandelman et. al, Single- and Multiple-Dose Study to Evaluate Pharmacokinetics, Safety and Tolerability in Healthy Volunteers: A Comparison of Extended-Release Oxycodone With Sequestered Naltrexone 40 mg Twice Daily to OxyContin 40 mg Twice Daily and Extended-Release Oxycodone With Sequestered Naltrexone 80 mg Once Daily. *Clinical Pharmacology in Drug Development* 4:361-369 (2015).

<sup>23</sup> The study does not specify whether it used Original OxyContin or Reformulated OxyContin. Given that the study was conducted in 2012, after Original OxyContin was discontinued in 2010, and the study states that the OxyContin at issue was obtained commercially, we believe it used Reformulated OxyContin.

mg twice daily, Troxyca ER 80 mg/9.6 mg once daily, and Reformulated OxyContin 40 mg twice daily in healthy volunteers. According to the study's authors,<sup>24</sup>

The primary objective was to characterize the pharmacokinetics (PK) of oxycodone following single- and multiple-dose oral administration of ALO-02 40 mg BID in healthy volunteers. Secondary objectives were to characterize (1) the PK of oxycodone following single- and multiple-dose administration of a comparator OxyContin (OXY-ER) 40 mg BID as well as an alternate regimen of ALO-02 80 mg QD, and (2) the safety and tolerability assessments.

Although a Reformulated OxyContin product was included as a comparator in the study, data from the Reformulated OxyContin arm of the study were not relied upon during FDA's evaluation of Pfizer's 505(b)(2) NDA. The comparisons Purdue cites from the published article were not relied on for approval of the 505(b)(2) NDA for Troxyca ER. The OxyContin arm of the study was only mentioned in the relevant NDA reviews for Troxyca ER as part of the study description. The study was not used to demonstrate the scientific relevance of the safety and effectiveness findings for Reformulated OxyContin to support approval of Troxyca ER (i.e., to establish a bridge between the two products), and it was not considered for that purpose.

Rather than relying upon the data on Reformulated OxyContin or relying on a comparison of that product with Troxyca ER to establish a bridge between the two products, FDA used data from the Troxyca ER arm of the study to evaluate the PK of the proposed drug product, both single- and multiple-dose. This information from the Troxyca ER arm of the study was necessary to establish the general PK profile of the product, including information about accumulation of the drug within the body, average concentrations, the time required for maximum concentrations ( $T_{max}$ ), and peak to trough fluctuations.

Accordingly, the Agency did not rely on previous findings of safety and effectiveness for Reformulated OxyContin (or otherwise rely on data regarding Reformulated OxyContin) in connection with this study to establish the safety and effectiveness of Troxyca ER. Thus, it is not necessary for Pfizer to cite Reformulated OxyContin as a listed drug in connection with this study to support approval of the Troxyca ER 505(b)(2) NDA.

## **2. Pfizer's Reliance on Roxycodone in the Troxyca ER 505(b)(2) NDA**

The Petition asserts that because Roxycodone is a 505(b)(2) NDA that relied upon a listed drug, Pfizer must also reference the listed drug that was relied upon for approval of the Roxycodone application. In support of that argument, the Petition cites a footnote in the Agency's 2004 Fenofibrate Petition Response. Petition at 13, note 27. The cited portion of the Fenofibrate Petition Response states:

Where a 505(b)(2) [NDA] seeks to rely on the finding of safety or effectiveness for a listed drug that is a 505(b)(2) NDA which, itself, relied on a previous finding of safety and effectiveness, the 505(b)(2) applicant should certify to the patents of the 505(b)(2)

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<sup>24</sup> See Gandelman at 1.

NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval. This is analogous to the requirement that an ANDA applicant referencing an approved suitability petition (or another ANDA approved pursuant to a suitability petition) certify to the patents for the approved NDA upon which the suitability petition or ANDA approval was based.<sup>25</sup>

### *FDA Response*

The FD&C Act together with the implementing regulations require a patent certification by the pending 505(b)(2) applicant only with respect to patents that are listed for the drug product on whose finding of safety and effectiveness the applicant relies. Thus, when a pending 505(b)(2) NDA relies for approval on a different sponsor's previously-approved 505(b)(2) NDA, the pending 505(b)(2) applicant is required only to certify to patents of the listed drug that it relies on.<sup>26</sup> FDA does not require the sponsor of the pending 505(b)(2) NDA to certify to patents that a different sponsor's previously-approved listed drug may, itself, have relied on when seeking its initial approval.<sup>27</sup>

As a result, Pfizer was not required to cite and certify to patents for any listed drug that Roxycodone relied upon for approval. Although the footnote text Purdue cited appears in the Fenofibrate Petition Response, the Agency's response addressed different facts and circumstances; and the issue implicated by the footnote was not squarely before the Agency.<sup>28</sup>

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<sup>25</sup> Fenofibrate Petition Response at 10, note 14.

<sup>26</sup> See e.g., Fenofibrate Petition Response at 6 (stating that the language of section 505(b)(2) of the FD&C Act explicitly links the drug relied on for approval to the drug for which patent certifications must be made); *Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell*, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015) (holding that the applicant need only certify to the product patents or the method-of-use patents that are associated with the reference listed drug (i.e., the drug product on whose finding of safety and effectiveness the 505(b)(2) applicant relies)), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

<sup>27</sup> Similarly, FDA's regulations require sponsors to certify only to patents for the listed drug upon which the applicant relies. See 21 CFR 314.50(1)(i) (requiring certification to patents for the drug relied on that are listed pursuant to 21 CFR 314.53, i.e., patents in the Orange Book). Absent this limitation, it could be unmanageable for sponsors to determine which of many possible generations of patents would need to be certified to when submitting a 505(b)(2) NDA.

<sup>28</sup> *Id.* at 1. In the Fenofibrate Petition Response, the Agency addressed, and denied, the petitioner's request that a 505(b)(2) applicant must certify to patents on all later-approved products that were approved based, in part, on some or all of the same underlying investigations as the listed drug relied upon. In a more recent citizen petition response, the Agency acknowledged that the Fenofibrate Petition did not raise the issue discussed in the cited footnote and provided additional clarification regarding the footnote text as follows:

[A]lthough we noted in the Fenofibrate Petition Response that a 505(b)(2) applicant seeking approval for a drug product that relies upon FDA's finding of safety and/or effectiveness for a drug product approved through the 505(b)(2) pathway "*should* certify to the patents of the 505(b)(2) NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval" (Fenofibrate Petition Response at 10, n. 14) (emphasis added), this was not the situation at issue in the Fenofibrate Petition. We subsequently have *required* an appropriate patent certification or statement to an "underlying NDA" only if the subsequent 505(b)(2) applicant specifically relied for approval on the drug product approved in the underlying NDA. . .

The Agency's conclusion for Troxyca – that Pfizer was not required to cite and certify to patents for any listed drug that Roxicodone relied upon for approval – is consistent with the FD&C Act and implementing regulations, the Fenofibrate Petition Response more generally (and related court case),<sup>29</sup> and the 2010 response to a citizen petition filed by Osmotica Pharmaceutical Corporation.

Pfizer's 505(b)(2) NDA for Troxyca ER relies on the Agency's previous finding of safety and effectiveness for Roxicodone (a 505(b)(2) NDA). The NDA holder for Roxicodone is Mallinckrodt, not Pfizer. Because the NDA holders are different, FDA does not consider Pfizer to be relying on any listed drug that Roxicodone relied on, and Pfizer is not required to certify to patents for any such underlying listed drug.<sup>30</sup>

In contrast, as noted in the Osmotica Petition Response, when a pending 505(b)(2) applicant cross-references (or incorporates by reference) its own 505(b)(2) NDA, it may continue to rely on the listed drug relied upon by its own cross-referenced 505(b)(2) NDA.<sup>31</sup> Thus, a sponsor's cross-reference to its own 505(b)(2) NDA may trigger additional patent certification obligations. Under these circumstances, the pending 505(b)(2) applicant cannot use its own cross-referenced 505(b)(2) NDA to circumvent its patent certification obligations to the original listed drug, if it relies on the original listed drug again for approval of its pending 505(b)(2) NDA.<sup>32</sup>

Pfizer cross-references (or incorporates by reference) its own 505(b)(2) NDA for Embeda, which relies on the Agency's findings of safety and effectiveness for Revia. Thus, Pfizer also relies on Revia and was expected to comply with patent certification provisions. In this case, Pfizer submitted a certification of no relevant patents.

For the reasons discussed above, Pfizer, by virtue of its reliance on Roxicodone, is not also required to reference any listed drug relied upon by Roxicodone or certify to those patents.<sup>33</sup>

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FDA Response to Osmotica Pharmaceutical Corporation, Docket No. FDA-2009-P-0356 (January 21, 2010) (Osmotica Petition Response) at 9-10 (footnotes omitted).

<sup>29</sup> Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

<sup>30</sup> The Petition also asserts that the approval history of Roxicodone indicates that Roxicodone relied upon Original OxyContin as the listed drug, even though Percodan was the drug referenced in the Roxicodone application. Petition at 13-28. We need not address these assertions for the purposes of this response because, even assuming *arguendo* Roxicodone relied on Original OxyContin, we would not require Pfizer to certify to patents of any listed drug that Roxicodone relied upon for approval for the reasons described above.

<sup>31</sup> Osmotica Petition Response at 9-10 (footnotes omitted); see also Proposed Rule titled *Abbreviated New Drug Applications and 505(b)(2) Applications*, 80 FR 6802, 6854-55 (February 6, 2015).

<sup>32</sup> *Id.*

<sup>33</sup> To the extent that Purdue asserts that Pfizer must identify Reformulated OxyContin as a listed drug because the application for Reformulated OxyContin currently contains data from the Original OxyContin application (Petition at 28), we note that the Agency has previously rejected a similar argument in the Fenofibrate Petition Response for the reasons described therein. See, e.g., Fenofibrate Petition Response at 6 (stating that the "phrase 'the drug for which such investigations were conducted' neither implicitly nor explicitly requires certification to patents on 'future formulations whose approval the investigations may support.'")

### 3. Pfizer's Reliance on Roxicodone and Revia in the Absence of a Pharmaceutical Equivalent

In addition to arguing that Pfizer must reference Reformulated OxyContin in its application for Troxyca ER, the Petition contends that Pfizer must reference the Agency's finding of safety and effectiveness for Targiniq ER because it is the drug "most similar" to Troxyca ER. Quoting language from the Fenofibrate Petition Response, the Petition argues that "when a section 505(b)(2) [NDA] has been submitted and no pharmaceutically equivalent drug product has been previously approved, the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought." Petition at 28-29, quoting the Fenofibrate Petition Response at 9-10.

The Petition acknowledges that in a 2013 citizen petition response,<sup>34</sup> FDA stated that the 2004 Fenofibrate Petition Response described a suggested approach that may enhance efficiency, but noted that listing the "most similar" drug is not required. Petition at 29. The Petition essentially asks that this policy be revisited to advance policy considerations, such as avoiding unnecessary research, allowing for efficient review by FDA, and to further the goals of the Hatch-Waxman Amendments. *Id.* at 30-34.

#### *FDA Response*

FDA has previously stated that if there is a listed drug that is a "pharmaceutical equivalent"<sup>35</sup> to the proposed drug product, the applicant should identify the pharmaceutically equivalent product as a listed drug relied upon and provide patent certifications for the patents listed for the pharmaceutically equivalent drug.<sup>36</sup> There is no listed drug that is a pharmaceutical equivalent to Troxyca ER, a fact that is not disputed in the Petition.

There is no statutory or regulatory requirement that an applicant rely upon the "most similar" product in its 505(b)(2) NDA as the Petition requests. Rather, "a sponsor interested in submitting a 505(b)(2) [NDA] that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs should determine which listed drug(s) is most appropriate for its development program."<sup>37</sup> Courts have recently upheld FDA's position on this issue.<sup>38</sup> If the applicant intends to submit a 505(b)(2) NDA that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, the applicant must establish that reliance on the

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<sup>34</sup> FDA Response to Hyman, Phelps, & McNamara, P.C. (September 18, 2013) (Docket Nos. FDA-2011-P-0869 and FDA-2013-P-0995) (Suboxone Petition Response).

<sup>35</sup> 21 CFR 320.1(c).

<sup>36</sup> Draft 505(b)(2) Guidance at 8; see also 80 FR 6802, 6855-56.

<sup>37</sup> Suboxone Petition Response at 7.

<sup>38</sup> *Takeda Pharmaceuticals, U.S.A., Inc. v. Burwell*, 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015), *affirmed*, No. 15-5021 (D.C. Cir. July 15, 2016).

listed drug(s) is scientifically appropriate and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s).<sup>39</sup>

Even if an applicant was required to list the “most similar” drug in a 505(b)(2) NDA, which it is not, it is not clear that Targiniq ER would have been the most similar drug in this case. As we have stated, “the determination of which listed drug is ‘most similar’ to a proposed product may be difficult (except in cases in which a pharmaceutical equivalent previously has been approved) and dependent on the sponsor’s approach to its development program.”<sup>40</sup> The Petitioner argues that Targiniq ER is the “most similar” product to Troxyca ER due to a number of similarities between the products,<sup>41</sup> including their active analgesic ingredient, extended-release properties, twice-daily administration, and indication. As noted in the Petition, however, there are a number of differences between the two products. Targiniq ER and Troxyca ER are different dosage forms (capsule versus tablet), use different opioid receptor antagonists (naltrexone versus naloxone), and work in different ways with regard to the opioid antagonist (Troxyca ER sequesters the antagonist while Targiniq ER does not). Petition at 35.

As discussed above, Pfizer chose to rely on the Agency’s finding of safety and effectiveness for Roxycodone and Revia and submitted appropriate support to bridge to the Agency’s safety and efficacy findings for those products. Pfizer’s approach was scientifically justified and followed statutory and regulatory requirements. In light of the foregoing, Pfizer is not required to rely upon Targiniq ER in its 505(b)(2) NDA for Troxyca ER.

#### **IV. CONCLUSION**

For the reasons described above, we believe the issues in the Petition have been adequately considered as they relate to the approval of Pfizer’s 505(b)(2) NDA for Troxyca; and they do not preclude approval or otherwise warrant additional actions with respect to the application.

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<sup>39</sup> Id.; Joint 505(b)(2) Petition Response at 12.

<sup>40</sup> Suboxone Petition Response at 7.

<sup>41</sup> Petition at 35.

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/s/  
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JOSHUA M LLOYD

08/19/2016

Refer to Page 1 of this document for the ORP signatures

SHARON H HERTZ

08/19/2016

## MEMORANDUM

TO: New Drug Application File for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) Extended Release Capsules (NDA 207621)

CC: Office of Regulatory Policy Citizen Petition File (FDA-2016-P-1946), Carol Bennett, Deborah Livornese (ORP), Curt Rosebraugh (ODE I), Ellen Fields (DAAAP), Gerald Dal Pan, Judy Staffa, Cynthia Kornegay (OSE), Doug Throckmorton (CDER)

FROM: Patrick Raulerson (Senior Regulatory Counsel, DRP IV, ORP) *PR*  
Sharon Hertz, MD (Division Director, DAAAP)

DATE: August 19, 2016

SUBJECT: Citizen Petition from Collegium Pharmaceutical, Inc. re: oxycodone extended-release products (FDA-2016-1946)

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This memorandum summarizes the agency's current thinking regarding the issues raised in the pending citizen petition submitted under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by Collegium Pharmaceutical, Inc. (the Collegium petition) as they relate to FDA's approval of TROXYCA® ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules (Troxyca ER).

As explained in section III of this memorandum, FDA has determined that Troxyca ER is safe and effective and can be approved under section 505 of the FD&C Act. We have also determined that the issues raised in the Collegium petition do not preclude approval or otherwise alter that determination with respect to Troxyca ER.

FDA is still otherwise considering the issues raised in the Collegium petition, and intends to respond on or before the statutory deadline associated with the petition, November 28, 2016.

### I. Collegium Petition

The Collegium petition requests that FDA refuse to approve any pending new drug application (NDA) or supplemental NDA for an oxycodone extended-release (ER) drug product unless: (1) such drug product bears abuse-deterrence labeling, based on premarket studies conducted in Categories 1, 2, and 3 as identified in FDA's guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling* (April 2015),<sup>1</sup> (the Evaluation and Labeling Guidance); and (2) those studies show that the product's abuse-deterrent properties are "equivalent or superior to" Xtampza ER (oxycodone) extended-release capsules (NDA 208090). (Collegium petition at 3.)

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<sup>1</sup> Available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>.

That is, these data must show, according to the petition, that “the [oxycodone ER] drug product is not less abuse-deterrent, and therefore, not less safe, than Xtampza ER.” (Collegium petition at 26.)

## **II. Troxyca ER**

Troxyca ER is the subject of NDA 207621 submitted pursuant to section 505(b)(2) of the FD&C Act. Troxyca ER is an extended-release oral dosage form opioid product containing two active ingredients: an opioid agonist (oxycodone hydrochloride) and a sequestered opioid antagonist (naltrexone hydrochloride). The product is designed to have abuse-deterrent properties as a result of the sequestered naltrexone.

Following a thorough analysis of the risks and benefits of the proposed product, including consideration of views of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee regarding whether the product should be approved for the proposed indication and whether it should be labeled with abuse-deterrent properties for the oral, intranasal, or intravenous routes of administration, FDA has determined that Troxyca ER meets the standard of approval for a new drug under section 505(c) of the FD&C Act for the conditions of use prescribed, recommended, or suggested in the labeling.

FDA is approving Troxyca ER for the management of pain severe enough to require daily, around the clock, long-term opioid treatment and for which alternative treatment options are inadequate, and with labeling stating that the product has abuse-deterrent properties that are expected to reduce abuse via the oral and intranasal routes. Specifically, FDA is approving labeling that summarizes the product’s abuse-deterrent properties as follows (in section 9.2 of the prescribing information):

The in vitro and pharmacokinetic data demonstrate that crushing TROXYCA ER pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data along with results from the oral and intranasal human abuse potential studies indicate that TROXYCA ER has properties that are expected to reduce abuse via the oral and intranasal routes. However, abuse of TROXYCA ER by these routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of TROXYCA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

A human abuse potential study of intravenous oxycodone HCl and naltrexone HCl to simulate crushed TROXYCA ER demonstrated lower Drug Liking and Take Drug Again Emax compared with oxycodone HCl alone. However, it is unknown whether these results with simulated crushed TROXYCA ER predict a reduction in abuse by the IV route until additional postmarketing data are available.

In determining that Troxyca ER’s benefits outweigh its risks, FDA has considered the fact that Troxyca ER, like the two other approved oxycodone ER products, has properties expected to result in a meaningful reduction in abuse, and therefore the data showing that the product can be expected to result in a meaningful reduction in that product’s abuse, together with an accurate

characterization of what the data mean, is included in the labeling for Troxyca ER (*See* Evaluation and Labeling Guidance standard at 22.)

FDA's rationale for approving Troxyca ER for the above-stated indication and with labeling describing the product's abuse-deterrent properties is set forth in the appropriate review documents, including Dr. Sharon Hertz's August 19, 2016, Summary Review for Regulatory Action. This memorandum focuses on FDA's determination that the issues raised in the Collegium petition do not preclude approval of or otherwise alter the agency's decision to approve Troxyca ER.

### **III. Discussion**

FDA is approving Troxyca ER with labeling describing its abuse-deterrent properties based on the full range of premarket studies, including Category 1 (in vitro), Category 2 (pharmacokinetic), and Category 3 (clinical abuse potential) studies, described the Evaluation and Labeling Guidance. As such, Troxyca ER's labeling is expected to include "abuse-deterrence labeling, based on premarket studies conducted in Categories 1, 2, and 3 identified in the [Evaluation and Labeling Guidance]." (Collegium petition at 3.)

FDA has concluded that both Xtampza ER and Troxyca ER can be expected to meaningfully deter abuse, and thus has approved (or, in the case of Troxyca ER, is approving) labeling for each describing the product's abuse-deterrent properties. However, at this time, the available pre-market data are not yet sufficient to assess the capacity of Troxyca to deter abuse relative to Xtampza ER in real world settings. We summarize below considerations and complexities involved in making such a determination.

#### **A. Postmarketing data are generally needed to assess the impact of abuse-deterrent properties in the community**

First, premarket data on abuse-deterrent properties generally allow FDA to determine that a product can be *expected* to deter abuse by one or more routes, but FDA requires that sponsors of all such products conduct postmarket studies to assess the actual impact of their products' abuse-deterrent properties on the prevalence and consequences of abuse. Accordingly, when labeling describing abuse-deterrent properties is based on premarket studies, it states only that the properties are "expected" to have an impact on abuse, and further explains that the labeling may be revised based on postmarketing experience. FDA explained the relationship between premarket and postmarket studies in the Evaluation and Labeling Guidance as follows:

[P]remarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling

should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies.

When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling. When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling. However, if these postmarket data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater risk (e.g., a shift from oral and nasal abuse to intravenous abuse), FDA may determine that labeling revisions are needed.

(Evaluation and Labeling Guidance at 22.)

For example, while the Troxyca ER premarket studies support a scientifically sound prediction that the drug product can be expected to meaningfully deter abuse by the oral and intranasal routes, such pre-market studies, generally speaking, do not support reliable predictions about the *precise extent* to which the product will deter abuse. Accordingly, Troxyca ER's labeling reports results from premarket clinical abuse potential studies, but the summary section of the labeling simply states that the product can be expected to deter abuse by the intranasal and oral routes. That is, the labeling does not include any quantitative assessment of the extent to which such abuse is expected to be deterred, because the available premarket data generally do not support such a prediction. Such data would likely be needed to do what is being asked by the petitioners.

Additionally, abuse-deterrent technologies vary significantly. For example, FDA has concluded that both Xtampza ER and Troxyca ER can be expected to meaningfully deter abuse, and thus has approved (or, in the case of Troxyca ER, is approving) labeling describing both products' abuse-deterrent properties. Xtampza ER's abuse-deterrent properties derive from the presence of excipients in the formulation that limit the effectiveness of physical and chemical manipulation intended to defeat the extended-release properties, whereas Troxyca ER's abuse-deterrent properties derive from the presence of sequestered naltrexone which is designed to be released into the blood if product is manipulated for purposes of abuse or misuse. Such differences complicate making inferences from pre-market testing regarding the relative safety of Troxyca ER and Xtampza.<sup>2</sup>

FDA intends to closely monitor and analyze all available postmarket data regarding abuse of Troxyca ER, as it does for all abuse-deterrent opioids, and may revise its labeling or take other regulatory action if warranted and appropriate.

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<sup>2</sup> It may be difficult to reach a conclusion about the relative safety of such products due, in part, to their different methods of abuse deterrence, as well as the myriad factors that may affect abuse in real world settings.

**B. FDA intends to continue to make regulatory decisions regarding Troxyca ER and other opioids on a case-by-case basis with appropriate consideration of available therapies and in a manner that is consistent with how we regulate drugs in other therapeutic areas**

FDA intends to continue to assess the benefit-risk profile of each opioid drug product, including its risk of abuse, on a case-by-case basis. It is also important to note that FDA takes into consideration available therapies as part of its risk benefit assessment of a drug. This approach is intended to balance the public health interest in the development of drug products with abuse-deterrent properties with the need to preserve access to a range of therapeutic agents (both brand-name and generic) for patients in pain.

In analyzing whether any drug product is safe and effective for its intended use, FDA conducts a benefit-risk analysis of the drug. To provide context for the drug-specific review, FDA considers the severity of the condition that the product is intended to treat, and the benefits and risks of other available therapies for the same condition. For example, Troxyca ER contains a fixed combination of oxycodone and naltrexone, while Xtampza ER contains only oxycodone as an active ingredient. As such, they may have different therapeutic benefits, such as for patients with hepatic impairment which may result in disproportionately higher levels of naltrexone relative to oxycodone.

The science of opioid use, abuse, and abuse deterrence is new and evolving. The agency's evolving scientific understanding of these issues may inform the scope of what drug products the agency considers available therapies, and the benefits and risks of those therapies relative to an opioid drug product under review.

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/s/  
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SHARON H HERTZ  
08/19/2016

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



**DATE:** 08/19/2016

**TO:** Targiniq (Oxycodone Hydrochloride and Naloxone Hydrochloride) ER tablets (new drug application (NDA) 205777)  
Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER capsules (NDA 207621)

**FROM:** CDER Exclusivity Board *Jay Soltani 8/19/16*

**THROUGH:** Sharon Hertz, MD, Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**SUBJECT:** Whether 3-Year Exclusivity for Targiniq (Oxycodone Hydrochloride and Naloxone Hydrochloride) ER tablets (NDA 205777) blocks the approval of Troxyca (Oxycodone Hydrochloride and Naltrexone Hydrochloride) ER tablets (NDA 207621)

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**SUMMARY**

This memorandum addresses whether the unexpired 3-year exclusivity for NDA 205777 for Targiniq extended-release (ER) tablets (Targiniq), a fixed-combination<sup>1</sup> that contains two active ingredients with the active moieties oxycodone and naloxone, blocks the approval of the 505(b)(2) NDA for Troxyca ER capsules (Troxyca) (NDA 207621), a fixed-combination that contains two active ingredients with the active moieties oxycodone and naltrexone.

The Exclusivity Board (Board) in the Center for Drug Evaluation and Research (CDER), in consultation with CDER's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

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<sup>1</sup> A drug containing two or more active ingredients in a single dosage form will be referred to as a fixed-combination in this memorandum, and a drug containing a single active ingredient will be referred to as a single-entity drug.

or Division) and other components of FDA, concludes that Targiniq’s 3-year exclusivity for the conditions of approval of NDA 205777 is tied to its specific combination of active moieties, oxycodone and naloxone. The Board thus recommends that any 3-year exclusivity for Targiniq should not block the approval of Troxyca because Troxyca has a different combination of active moieties, oxycodone and naltrexone.<sup>2</sup>

## I. LEGAL BACKGROUND

### A. Drug Approval Pathways Under the FD&C Act

Section 505 of the Federal Food, Drug & Cosmetic (FD&C) Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs). Because Targiniq and Troxyca are 505(b)(2) NDAs, the remaining discussion will focus primarily on the 505(b)(2) pathway.

#### 1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, “full reports of investigations” to show that the drug for which the applicant is seeking approval is safe and effective.<sup>3</sup> NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.<sup>4</sup> One basis for FDA not approving a 505(b)(1) NDA is that there is a lack of substantial evidence that the drug product is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.<sup>5</sup>

#### 2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)<sup>6</sup> amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs

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<sup>2</sup> This memorandum only discusses whether the 3-year exclusivity for Targiniq should block the approval of the Troxyca NDA, and does not address the full scope of Targiniq’s exclusivity nor whether Troxyca is eligible for its own period of exclusivity or the scope of any such exclusivity. This memorandum does not address naturally derived mixtures or other complex products.

<sup>3</sup> See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

<sup>4</sup> See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

<sup>5</sup> See section 505(d)(5) of the FD&C Act.

<sup>6</sup> Public Law 98-417 (1984).

and ANDAs, respectively.<sup>7</sup> The Hatch-Waxman Amendments reflect Congress’s efforts to balance the need to “make available more low cost generic drugs by establishing a generic drug approval procedure” with new incentives for drug development in the form of exclusivity and patent term extensions.<sup>8</sup> These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.<sup>9</sup>

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the “full reports” requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.<sup>10</sup> Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as its own studies, published reports of studies to which the applicant has no right of reference, the Agency’s findings of safety and/or effectiveness for one or more previously approved drugs, or a combination of these and other sources to support approval.<sup>11</sup>

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<sup>7</sup> Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously-approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

<sup>8</sup> See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

<sup>9</sup> See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

<sup>10</sup> Section 505(b)(2) of the FD&C Act provides for approval of an application:

for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

As defined at 21 CFR 314.3, “*Right of reference or use* means the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.”

<sup>11</sup> See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA’s transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity (NCE),<sup>12</sup> and, in some instances, may describe a drug product with substantial differences from a listed drug.<sup>13</sup> When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*<sup>14</sup> its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability<sup>15</sup> of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process,<sup>16</sup> the 505(b)(2) Draft Guidance, and previous citizen petition responses.<sup>17</sup> FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. FDA's interpretation of section 505(b)(2) avoids requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval, with no corresponding benefit to the public health. In addition, the conduct of duplicative studies may raise ethical concerns because it could subject human beings and animals to medically or scientifically unnecessary testing. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the drug on which the 505(b)(2) application seeks to rely.<sup>18</sup>

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<sup>12</sup> See 21 CFR 314.108(a) (defining *new chemical entity* as “a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [FD&C Act]”).

<sup>13</sup> In October 1999, the Agency issued a draft guidance for industry entitled “Applications Covered by Section 505(b)(2)” (505(b)(2) Draft Guidance) which states that “[a] 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference.” 505(b)(2) Draft Guidance at 3, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>14</sup> The “bridge” in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

<sup>15</sup> Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's Guidance for Industry: “Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations” (March 2014) (BA/BE NDA/IND Guidance), at 3.

<sup>16</sup> See Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989); Abbreviated New Drug Application Regulations, 57 FR 17950 (April 28, 1992); Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338 (October 3, 1994).

<sup>17</sup> See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

<sup>18</sup> 21 CFR 314.54(a) states that “[A 505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug.”

## B. Exclusivity Under the FD&C Act and Fixed-Combinations

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation in the form of 3-year and 5-year NCE exclusivity to protect qualified drugs submitted under section 505(b) from competition from certain 505(b)(2) NDAs and ANDAs for varying periods of time depending on the factual circumstances. Although our decision here relates specifically to 3-year exclusivity, we provide background first on 5-year NCE exclusivity for contextual purposes, followed by background on 3-year exclusivity, and then apply the framework to fixed-combinations.

### 1. 5-Year NCE Exclusivity

The longest and most protective period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity described at section 505(c)(3)(E)(ii) of the FD&C Act.<sup>19</sup> Under this section, a 5-year exclusivity period is provided for a drug “no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)].”<sup>20</sup> This exclusivity generally has been interpreted to prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug.<sup>21</sup> Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

FDA’s regulations at 21 CFR 314.108 implement the statutory exclusivity provisions. Under FDA’s interpretation of the statute, embodied in the regulations, a drug that contains an NCE

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<sup>19</sup> A parallel provision can be found at section 505(j)(5)(F)(ii).

<sup>20</sup> Section 505(c)(3)(E)(ii) of the Act provides:

If an application submitted under subsection (b) [of this section] for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) [of this section], is approved after [September 24, 1984], no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) [of this section] before the expiration of five years from the date of the approval of the application under subsection (b) [of this section], except that such an application may be submitted under subsection (b) [of this section] after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) [of this section]. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

See also section 505(j)(5)(F)(ii).

<sup>21</sup> An applicant may submit an ANDA or 505(b)(2) NDA after 4 years under specific circumstances described in section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act that are not at issue here.

will qualify for 5 years of NCE exclusivity. If a drug does not contain an NCE, it will not be eligible for 5-year NCE exclusivity, but it may be eligible for 3-year exclusivity.<sup>22</sup>

The Agency's regulations define *new chemical entity* to mean "a drug<sup>23</sup> that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the [FD&C Act]."<sup>24</sup> *Active moiety* in turn is defined as:

[T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.<sup>25</sup>

FDA's interpretation of the 5-year NCE exclusivity provisions has focused on the specific chemical structure of the active moiety under consideration;<sup>26</sup> FDA concluded that the term "active ingredient," as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," refers to the active moiety. FDA adopted a chemical structure-driven approach based upon certain reasonable, generally applicable scientific principles regarding the anticipated characteristics of different types of molecules, which can be applied consistently to different types of drugs.<sup>27</sup> Under this approach, the Agency does not need to determine the

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<sup>22</sup> Describing the 5-year NCE exclusivity provisions, Representative Waxman stated:

[T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. This provision will give the drug industry the incentives needed to develop **new chemical entities** whose therapeutic usefulness is discovered late when little or no patent life remains.

130 Cong. Rec. 24425 (1984) (statement of Rep. Waxman) (emphasis added). Representative Waxman contrasted this to 3-year exclusivity (which would be available for drugs that did not qualify for the longer period of exclusivity given to a new chemical entity) as follows:

[A] 3-year period of exclusive market life is afforded to **non-new chemical entities** approved after enactment of the bill which have undergone new clinical studies essential to FDA approval.

Id. (emphasis added). See also 130 Cong. Rec. 23765 (1984) (statement of Sen. Hatch).

<sup>23</sup> In FDA's guidance for industry entitled, "New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products" (Oct. 2014) (Fixed-Combination NCE Guidance), FDA explains that under its current thinking, the word "drug" in this phrase refers to the drug substance, not the drug product as FDA had previously interpreted the statute. We note that the terms "drug substance" and "active ingredient" are used interchangeably for purposes of this memorandum. See definition of *drug substance* at 21 CFR 314.3(b) and definition of *active ingredient* at 21 CFR 210.3(b)(7).

<sup>24</sup> 21 CFR 314.108(a).

<sup>25</sup> Id.

<sup>26</sup> See, e.g., Abbreviated New Drug Application Regulations, 54 FR 28872, 28897-28898 (July 10, 1989) ("1989 Proposed Rule").

<sup>27</sup> See, e.g., Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338, at 50358 (Oct. 3, 1994) ("1994 Final Rule") (concluding that the definition of active moiety should exclude chelates, clathrates, and other noncovalent derivatives because they generally do not affect the active moiety of a drug product).

precise molecule or molecules responsible for the pharmacological action in vivo to determine eligibility for 5-year NCE exclusivity.

Thus, in determining the eligibility for 5-year NCE exclusivity for a single-entity drug, FDA conducts a structure-based analysis on the active ingredient, and if the active ingredient contains an active moiety that the Agency has not previously approved, the drug will be eligible for 5-year exclusivity. Such exclusivity will block any application that contains the active moiety protected by 5-year NCE exclusivity.

## 2. 3-Year Exclusivity

The Hatch-Waxman Amendments also provide for a 3-year period of exclusivity for certain drugs that are not eligible for 5-year NCE exclusivity. The statute and regulations for 3-year exclusivity describe which original NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For original NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:<sup>28</sup>

*If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.<sup>29</sup>*

The first clause (italicized) in section 505(c)(3)(E)(iii), often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. As noted in Section I.B.1, in the 5-year NCE exclusivity context, FDA has interpreted the term “active ingredient” in the phrase “active ingredient (including any ester or salt of the active ingredient)” to mean active moiety. Under the eligibility clause in section 505(c)(3)(E)(iii), applications for single-entity drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety “that has been

<sup>28</sup> A parallel provision applies 3-year exclusivity to ANDAs. See section 505(j)(5)(F)(iii) of the FD&C Act.

<sup>29</sup> See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv) (similarly stating that if an application submitted under section 505(b) contains new clinical investigations that were essential to approval and conducted or sponsored by the applicant, the Agency “will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application . . .”).

approved in another application”) are eligible for 3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA’s implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity. Among other things, they define the terms *clinical investigation*,<sup>30</sup> *new clinical investigation*,<sup>31</sup> and *essential to approval*.<sup>32</sup>

The second clause in section 505(c)(3)(E)(iii) (underlined), often referred to as the bar clause, describes which 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity. The Agency’s interpretation of the bar clause and thus a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) generally involves two aspects. One aspect of the scope inquiry focuses on the drug at issue. The phrase “such drug in the approved subsection (b) application” in the bar clause refers to the earlier use of the term “drug” in the eligibility clause. The “drug” in the eligibility clause refers to “a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application,” that is, the drug which includes a previously approved active moiety. FDA interprets this cross reference to mean that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity.<sup>33</sup> Another aspect of the scope inquiry focuses on the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant informs the “conditions of approval” relevant to 3-year exclusivity.<sup>34</sup>

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<sup>30</sup> “Clinical investigation” is defined as “any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects.” 21 CFR 314.108(a).

<sup>31</sup> “New clinical investigation” is defined as “an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.” 21 CFR 314.108(a).

<sup>32</sup> “Essential to approval” means “with regard to an investigation, that there are no other data available that could support approval of the application.” 21 CFR 314.108(a).

<sup>33</sup> See Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, M.D., President & CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. and Ralph S. Tyler, Esq., Venable L.L.P. (Oct. 5, 2015) (Docket No. FDA-2015-P-2482), aff’d *Otsuka Pharmaceutical Co., Ltd., et al v. FDA*, Case No. 1:15-cv-01688-KBJ (D.D.C. July 28, 2016) (upholding FDA’s interpretation of section 505(c)(3)(E)(iii) that, for a single-entity drug to be potentially barred by 3-year exclusivity for another single-entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity) (currently pending appeal).

<sup>34</sup> FDA considered, in the context of a single-entity drug, the meaning of the phrase “conditions of approval of such drug in the approved subsection (b) application” in a recent decisional letter regarding whether Astellas’ 3-year exclusivity for its tacrolimus drug, Astagraf XL, blocks approval of Veloxis’ tacrolimus drug, Envarsus XR. See Letter from R. Albrecht, FDA to M. McGuinness, Veloxis Pharmaceuticals, Inc., Jan. 12, 2015 (Veloxis Letter), aff’d *Veloxis Pharmaceuticals, Inc. v. FDA*, No. 14-cv-2126, 2015 U.S. Dist. LEXIS 77559 (D.D.C. June 12, 2015) (“Veloxis Court Decision”). In the Veloxis Letter, FDA considered both aspects of the scope inquiry in determining whether approval of Envarsus XR was blocked. Although not a subject of dispute, it was clear that in interpreting the phrase “conditions of approval of such drug in the subsection (b) application,” FDA considered the conditions of approval for tacrolimus, which was the single active moiety for the two products at issue. In the Veloxis Letter, FDA repeatedly stated that the exclusivity for Astagraf XL covered “a once-daily, extended-release

Thus, in the case of an application submitted for a single-entity drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval (i.e., the conditions of approval for which new clinical investigations were essential).

For supplements to approved NDAs, section 505(c)(3)(E)(iv) of the FD&C Act states:

*If a supplement to an application approved under subsection (b) [of this section] is approved after [September 24, 1984,] and the supplement contains reports of new clinical investigations (other than bioavailability [sic] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) [of this section] . . . . [(emphasis added)].*

Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA and a supplement to an NDA, FDA has taken a consistent approach to both types of applications in determining eligibility for 3-year exclusivity and scope. The eligibility clause in section 505(c)(3)(E)(iv) (italicized) corresponds to the eligibility clause in section 505(c)(3)(E)(iii) of the FD&C Act, except, among other things, in section 505(c)(3)(E)(iv), the word “supplement” is substituted for the word “application” in section 505(c)(3)(E)(iii). As with an original NDA, a supplement may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement.

The bar clause of section 505(c)(3)(E)(iv) (underlined) describes 3-year exclusivity as blocking approval of a 505(b)(2) application for “a change approved in the supplement.” Although this language is not identical to the phrase “conditions of approval of such drug in the approved subsection (b) application” used in section 505(c)(3)(E)(iii), in determining the scope of exclusivity and which applications are barred, there are likewise two aspects of the inquiry. One aspect of the inquiry focuses on the drug at issue. Under FDA’s longstanding policy regarding which changes are eligible to be approved in a supplement (as opposed to requiring a full, new original application), any change in the active ingredient (and thus any change in active moiety)

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dosage form of tacrolimus for prophylaxis of organ rejection for use in de novo kidney transplant patients.” FDA did not consider other single-entity drugs that contained a different active moiety in determining whether Envarsus XR’s approval would be blocked. Because the active moiety was the same for the two products at issue, FDA then considered the scope of the new clinical investigations essential to the approval conducted or sponsored by the applicant to determine the “conditions of approval of such drug” and thus the scope of exclusivity.

may only be made through a new, original application, not a supplement.<sup>35</sup> In other words, a change approved in a supplement must be a change in conditions of approval for the same drug (active moiety) approved in the original NDA. Thus, in order to determine that a 505(b)(2) NDA is blocked because it seeks approval for a “change approved in a supplement” during another applicant’s 3-year exclusivity period, FDA interprets the 505(c)(3)(E)(iv) language such that the 505(b)(2) NDA must be for a drug with the same active moiety as the drug with exclusivity.

If the 505(b)(2) application for a single-entity drug seeks approval for the same drug (active moiety) to which exclusivity has attached, then the second aspect of the scope inquiry applies. To determine whether the 505(b)(2) NDA is barred, FDA must also determine what exclusivity-protected change was approved in the supplement. To do so, FDA examines the conditions of approval supported by the new clinical investigations (other than bioavailability studies) that were essential to approval of the supplement. If the 505(b)(2) NDA for a single-entity drug is for the same drug for the same exclusivity-protected change approved in the supplement, it will be blocked.

### 3. *5-Year NCE Exclusivity, 3-Year Exclusivity, and Fixed-Combinations*

The 5-year NCE exclusivity and 3-year exclusivity statutory and regulatory provisions apply not only to single-entity drugs, but also to fixed-combinations. When FDA evaluates a fixed-combination to determine eligibility for 5-year NCE exclusivity, it conducts a structure-based chemistry analysis to determine whether any of the individual active ingredients in the fixed-combination contains an active moiety that has never previously been approved. If the fixed-combination contains an active ingredient that includes a previously unapproved active moiety, that active ingredient is considered an NCE, and 5-year NCE exclusivity attaches to the previously unapproved active moiety. In such a case (with certain exceptions not relevant here) applications for drugs containing that active moiety are barred from submission for a period of 5 years.<sup>36</sup>

As noted in Section I.B, FDA considers eligibility for 3-year exclusivity only if it has determined that 5-year NCE exclusivity is not available. Thus, if after conducting its structure-based chemistry analysis, FDA determines that no active ingredient in the fixed-combination contains an active moiety that has not been previously approved, (i.e., it determines that no 5-year NCE exclusivity will attach), the Agency will then proceed with determining eligibility of the fixed-combination for 3-year exclusivity. In analyzing eligibility for 3-year exclusivity for a fixed-combination, the Agency determines whether the fixed-combination or a change to the fixed-combination is supported by new clinical investigations (other than bioavailability studies) essential to approval of the application for the fixed-combination (or the supplement to the application for the fixed-combination) and were conducted or sponsored by the applicant.

505(b)(2) NDAs are barred from approval by 3-year exclusivity for an original application if

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<sup>35</sup> See FDA’s guidance for industry entitled “Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees”, at 3 (Bundling Guidance) (“Every different active ingredient or combination of two or more different active ingredients should be submitted in a separate original application.”).

<sup>36</sup> See Fixed-Combination NCE Guidance at 8.

they are seeking approval for “the conditions of approval of such drug.” In the case of a fixed-combination, when determining which applications are seeking approval for “the conditions of approval of such drug” and thus have the potential to be blocked, FDA generally focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination. This is because the clinical investigations that earn exclusivity must be submitted to the application for the combination, and necessarily support approval of the combination described in the application (or of a change to that combination).<sup>37</sup> Thus, the conditions of approval of *such drug* necessarily encompass the conditions of approval of the particular combination of active moieties of the drug for which the application was submitted and for which new clinical investigations were essential.

Similarly, applications are barred from approval by 3-year exclusivity for a supplement if they are seeking approval for the “change approved in the supplement.” As noted in Section I.B.2, FDA interprets 3-year exclusivity for a supplement to provide the same protection as 3-year exclusivity for an original application. Thus, in determining whether a 505(b)(2) NDA is seeking approval for a “change approved in the supplement” to a fixed-combination and is therefore blocked by 3-year exclusivity for the supplement, FDA similarly focuses its inquiry to applications that contain the same combination of active moieties as in the fixed-combination and examines the scope of the new clinical investigations essential to the approval and that were conducted or sponsored by the applicant. If the 505(b)(2) NDA is seeking approval for a fixed-combination with a different combination of active moieties than the combination with exclusivity, it is not seeking approval for a change approved in the supplement and therefore cannot be blocked.

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<sup>37</sup> FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each drug in the fixed-combination be shown to contribute to efficacy. It is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. See 21 CFR 300.50.

## II. FACTUAL BACKGROUND

### A. Targiniq<sup>38</sup>

Purdue Pharma L.P.'s (Purdue's) NDA for Targiniq ER tablets (NDA 205777) was approved by FDA on July 23, 2014. Targiniq is a fixed-combination comprising two active moieties: oxycodone (from the active ingredient oxycodone HCl) and naloxone (from the active ingredient naloxone HCl). Targiniq ER tablets are intended for oral administration every 12 hours, and are available in dosage strengths (oxycodone/naloxone milligrams (mg)) 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg.<sup>39</sup>

Oxycodone is a  $\mu$ -opioid receptor agonist (with some activity at the  $\kappa$  and  $\delta$  receptors) with the primary therapeutic action of analgesia. Oxycodone has been marketed for over 80 years. Oxycodone is an active moiety in several marketed drug products used for the treatment of pain, including as a single-entity product<sup>40</sup> and in combination with acetaminophen or non-steroidal anti-inflammatory drugs.<sup>41</sup>

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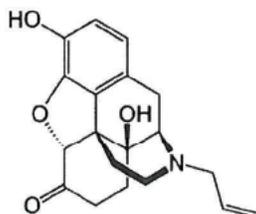
<sup>38</sup> There are other drug products containing oxycodone with unexpired exclusivity. OxyContin (oxycodone HCl) ER tablets (OxyContin) (NDA 022272) is a single-entity drug that contains one active ingredient with the active moiety oxycodone. On August 13, 2015, FDA approved a supplement (S-027) to the OxyContin NDA. That approval included labeling changes regarding the use of OxyContin in the pediatric population. S-027 qualified for 3-year exclusivity which will expire on August 13, 2018. Xtampza ER (oxycodone) ER capsules (NDA 208090) is a single-entity drug that contains one active ingredient with the active moiety oxycodone. On April 26, 2016, FDA approved the NDA for Xtampza ER, and the NDA qualified for 3-year exclusivity which will expire on April 26, 2019. Xartemis XR (oxycodone HCl and acetaminophen) ER tablets (NDA 204031) is a fixed-combination that contains two active ingredients with the active moieties oxycodone and acetaminophen. On March 11, 2014, FDA approved an original 505(b)(2) NDA for Xartemis XR, and the NDA qualified for 3-year exclusivity which will expire on March 11, 2017. We do not need to address the full scope of any applicable exclusivity for OxyContin, Xtampza ER, or Xartemis XR to recommend that any exclusivity for OxyContin, Xtampza ER, and Xartemis XR should not block the approval of the Troxyca NDA. The first aspect of the scope inquiry as described in Section I.B is determinative. OxyContin and Xtampza ER contain only a single active moiety (oxycodone), whereas Troxyca contains a combination of active moieties (oxycodone and naltrexone). Because Troxyca is a fixed-combination whereas OxyContin and Xtampza ER are single-entity drugs, any approval of Troxyca is not an approval for the "change approved in the supplement" for which OxyContin has exclusivity or for the "conditions of approval of such drug in the approved subsection (b) application" for which Xtampza ER has exclusivity. Also, Xartemis XR contains a combination of two active moieties (oxycodone and acetaminophen), whereas Troxyca contains a different combination of two active moieties (oxycodone and naltrexone). Because Troxyca does not contain the same combination of active moieties approved in Xartemis XR, any approval of Troxyca is not an approval for the "conditions of approval of such drug in the approved subsection (b) application" for which Xartemis XR has exclusivity. Therefore, we recommend that any applicable exclusivity for OxyContin, Xtampza ER, or Xartemis XR should not block the approval of Troxyca. We need not analyze the second aspect of the scope inquiry as described in Section I.B. In addition, we need not examine whether any additional drug products containing naloxone have unexpired exclusivity because Troxyca does not contain the active moiety naloxone.

<sup>39</sup> NDA 205777, Targiniq Cross Discipline Team Leader (CDTL) Review at 2 (July 14, 2014). See also Targiniq Product Labeling approved July 23, 2014.

<sup>40</sup> See, e.g., OxyContin ER tablets (NDA 022272), Oxaydo tablets (NDA 202080), and numerous generic versions.

<sup>41</sup> See, e.g., Percocet tablets (currently marketed under numerous ANDAs) and Percodan tablets (NDA 007337).

Naloxone, (5R,9R,13S,14S)-17-Allyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one (molecular formula, C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>),<sup>42</sup> is a nonselective<sup>43</sup> opioid receptor antagonist that markedly attenuates or completely blocks the subjective effects of opioids such as oxycodone through reversible, competitive binding at  $\mu$ -opioid receptors. Naloxone can exert an effect anywhere there are opioid receptors such as in the brain, spinal cord, and peripheral organs (e.g., intestine, heart, kidney, and lungs). Naloxone will precipitate withdrawal symptoms in subjects physically dependent on opioids. Naloxone is a congener of oxymorphone with no opioid agonist properties of its own. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.<sup>44</sup> The structure of naloxone is shown below.



Naloxone was first approved on April 13, 1971 as Narcan (NDA 016636), a parenteral product to reverse the effects of opioid overdose. When administered orally, the absolute bioavailability of naloxone is less than 2% due to extensive first-pass metabolism in the liver. Naloxone has since been approved as two additional single-entity products<sup>45</sup> and in combination with pentazocine to deter parenteral abuse.<sup>46</sup> Naloxone is also approved in combination with buprenorphine for maintenance treatment for opioid dependence.<sup>47</sup>

Targiniq was approved by FDA 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”<sup>48</sup> on July 23, 2014. The 505(b)(2) NDA for Targiniq relied, in part, on FDA’s previous finding of safety and effectiveness for Narcan and cross-referenced Purdue’s OxyContin (oxycodone HCl) products – original OxyContin (NDA 20553) and reformulated OxyContin (NDA 022272). Targiniq is a fixed-combination comprising the active moieties oxycodone and naloxone. The extended-release mechanism of Targiniq is matrix-controlled with stearyl alcohol and ethylcellulose N45 as rate controlling excipients.<sup>49</sup>

<sup>42</sup> In Targiniq naloxone is present as its HCl salt form.

<sup>43</sup> In some cases, naloxone shows greater selectivity for the  $\mu$ -opioid receptor than the  $\delta$ - or  $\kappa$ -opioid receptor.

<sup>44</sup> In contrast, naltrexone differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.

<sup>45</sup> See Evzio (NDA 205787) and Narcan Nasal Spray (NDA 208411).

<sup>46</sup> See Talwin NX (NDA 018733).

<sup>47</sup> See, e.g., Suboxone (NDA 020733) and Bunavail (NDA 205637).

<sup>48</sup> Targiniq falls within the class of drugs that are part of the Extended-Release/Long-Acting (ERLA) Opioid Risk Evaluation and Mitigation Strategy (REMS), and the indication is the same as that for other ERLA products. Targiniq CDTL Review at 2.

<sup>49</sup> NDA 205777, Targiniq Controlled Substances Staff (CSS) Review at 8 (June 24, 2014).

The intent of the addition of naloxone to the Targiniq formulation is to provide abuse-deterrent (AD) properties as described in NDA 205777.<sup>50</sup> The principal mechanism underlying the AD properties of Targiniq is the effectiveness of the 2:1 oxycodone:naloxone ratio in blocking the subjective reinforcing effects of oxycodone administered by the intranasal and intravenous routes and potentially precipitating withdrawal.<sup>51</sup> As shown by in vitro studies, the difficulty involved in separating naloxone from oxycodone also contributes to Targiniq's AD properties. Targiniq is not formulated (i) to be resistant to crushing; (ii) to resist, upon crushing, compromise of the controlled-release properties of oxycodone or naloxone;<sup>52</sup> or (iii) to gel upon exposure to an aqueous environment, as there are no gelling agents in the formulation.<sup>53</sup>

Purdue demonstrated the efficacy of Targiniq in a single, adequate, and well-controlled clinical trial, Study ONU3701. This clinical trial was conducted as a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm enriched design study in opioid-experienced patients with chronic low back pain who required around-the-clock opioids in a range of 20 mg to 160 mg morphine equivalents.<sup>54</sup>

This study was necessitated by the inclusion of naloxone in Targiniq. Specifically, the Division advised Purdue that as a 505(b)(2) applicant relying on the Agency's finding of safety and efficacy for Narcan, with cross-reference to Purdue's original OxyContin and reformulated OxyContin NDAs, it would need to conduct a clinical trial demonstrating efficacy if detectable levels of naloxone in systemic circulation were noted.<sup>55</sup> Among other concerns, the Agency was concerned about the potential impacts of naloxone on the analgesic efficacy of oxycodone<sup>56</sup> (in particular whether the presence of naloxone could interfere with analgesic efficacy), and recognized the possibility that patients treated with Targiniq may be at risk for adverse events due to the presence of naloxone, specifically opioid withdrawal.<sup>57</sup> Study ONU3701 was prospectively designed to evaluate efficacy and to assess the occurrence of opioid withdrawal symptoms in subjects treated with Targiniq compared to placebo.

Purdue also conducted certain studies to evaluate the AD properties of Targiniq. For instance, Purdue conducted several human abuse potential studies (Studies ONU1003, ONU1004,

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<sup>50</sup> Targiniq CDTL Review at 2-3; NDA 205777, Targiniq Clinical Review at 8 (June 18, 2014); NDA 205777, Targiniq Summary Review at 3 (July 23, 2014).

<sup>51</sup> Targiniq Summary Review at 26, citing Targiniq CSS Review at 3.

<sup>52</sup> Simple crushing of the tablets results in rapid and complete compromise of the controlled release properties of oxycodone and naloxone.

<sup>53</sup> Targiniq CSS Review at 3.

<sup>54</sup> Targiniq Clinical Review at 9.

<sup>55</sup> Targiniq CDTL Review at 19.

<sup>56</sup> Targiniq PIND 70851, Meeting Minutes for February 24, 2009, Pre-IND Meeting at 8. See also, Targiniq PIND 70851, Written Response from FDA to Purdue (August 19, 2011) at 1-2.

<sup>57</sup> Targiniq Summary Review at 20, citing CDTL Review at 30-35.

ONU1007, and ONU1008) to assess Targiniq's resistance to abuse by intravenous (IV), intranasal, and oral administration.<sup>58</sup>

Targiniq has 3-year exclusivity which will expire on July 23, 2017. The exclusivity is denoted in the Orange Book as "new combination" (NC). FDA has concluded that some of the clinical studies submitted in the Targiniq NDA qualified for 3-year exclusivity because they were new clinical investigations essential to approval of the NDA and were conducted by Purdue.<sup>59</sup> However, we need not determine the full scope of that exclusivity to recommend that Targiniq's exclusivity should not block approval of Troxyca as discussed below.

## **B. Troxyca<sup>60</sup>**

NDA 207621 for Troxyca ER capsules was submitted by Pfizer, Inc. (Pfizer) on December 19, 2014. Pfizer is seeking approval of Troxyca 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. Troxyca is a fixed-combination comprising two active moieties: oxycodone (from the active ingredient oxycodone HCl) and naltrexone (from the active ingredient naltrexone HCl). The product is intended for oral administration every 12 hours, and is available in dosage strengths (oxycodone/naltrexone mg) of 10 mg/1.2 mg; 20 mg/2.4 mg; 30 mg/3.6 mg; 40 mg/4.8 mg; 60 mg/7.2 mg; and 80 mg/9.6 mg.

Naltrexone, (5 $\alpha$ )-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (molecular formula, C<sub>20</sub>H<sub>23</sub>NO<sub>4</sub>)<sup>61</sup> is a nonselective opioid receptor antagonist that markedly

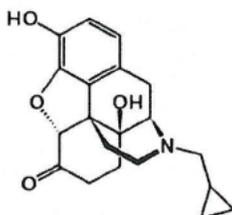
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<sup>58</sup> Targiniq CSS Review, generally. See also, Targiniq Clinical Review at 106, Targiniq Summary Review at 30-32.

<sup>59</sup> FDA intends to reach a decision on these matters during the ordinary course of making exclusivity decisions in relation to other applications for combinations of oxycodone and naloxone as appropriate. Such a determination would require the Agency to identify the new clinical investigations that were essential to approval and to determine the conditions of approval resulting from those new clinical investigations.

<sup>60</sup> There are other fixed-combinations containing naltrexone with unexpired exclusivity. Embeda (morphine sulfate and naltrexone HCl) ER capsules (NDA 022321) is a fixed-combination that contains two active ingredients with the active moieties morphine and naltrexone. FDA approved the original NDA for Embeda on August 13, 2009. On October 17, 2014, FDA approved a supplement (S-016) to the Embeda NDA. That approval included labeling changes regarding the AD properties of Embeda. S-016 qualified for 3-year exclusivity which will expire on October 17, 2017. Contrave (naltrexone HCl and bupropion HCl) ER tablets (NDA 200063) is a fixed-combination that contains two active ingredients with the active moieties naltrexone and bupropion. On September 10, 2014, FDA approved an original 505(b)(2) NDA for Contrave, and the NDA qualified for 3-year exclusivity which will expire on September 10, 2017. We do not need to address the full scope of any applicable exclusivity for Embeda or Contrave to recommend that any exclusivity for Embeda and Contrave should not block the approval of the Troxyca NDA. The first aspect of the scope inquiry as described in Section I.B is determinative. Embeda contains a combination of two active moieties (morphine and naltrexone) and Contrave contains a combination of two active moieties (naltrexone and bupropion), whereas Troxyca contains a different combination of two active moieties (oxycodone and naltrexone). Because Troxyca does not contain the same combination of active moieties approved in Embeda or Contrave, any approval of Troxyca is not an approval for the "change approved in the supplement" for which Embeda has exclusivity or for the "conditions of approval of such drug in the approved subsection (b) application" for which Contrave has exclusivity. Therefore, we recommend that any applicable exclusivity for either Embeda or Contrave should not block the approval of Troxyca. We need not analyze the second aspect of the scope inquiry as described in Section I.B.

attenuates or completely blocks the subjective effects of opioids such as oxycodone through reversible, competitive binding at  $\mu$ -opioid receptors. Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties.<sup>62</sup> Naltrexone will precipitate withdrawal symptoms in subjects physically dependent on opioids.<sup>63</sup> Structurally, naltrexone is a congener of oxycodone with no opioid agonist properties of its own. It differs from oxycodone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.<sup>64</sup> The structure of naltrexone is shown below.



Naltrexone was first approved as Naltrexone HCl on November 20, 1984 (Revia Tablets; NDA 018932)<sup>65</sup> for the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. With regard to treating opioid dependence, naltrexone has since been approved as a single-entity product (Vivitrol; NDA 021897 approved on April 13, 2006). Naltrexone has also been approved as part of a fixed-combination with morphine sulfate intended to provide AD properties (Embeda; NDA 022321 approved on August 13, 2009).

NDA 207621 for Troxyca was submitted pursuant to section 505(b)(2) of the FD&C Act, and relies, in part, on FDA's findings of safety and effectiveness for Roxycodone (oxycodone HCl) (NDA 021011) and Revia (naltrexone HCl) (NDA 018932). Pfizer also cross-referenced its NDA 022321 for Embeda (morphine sulfate and naltrexone HCl).

In contrast with naloxone, naltrexone is generally well-absorbed orally, and is bioavailable to a greater extent. Like naloxone, naltrexone is subject to significant first pass metabolism in the liver; however, its absolute oral bioavailability is estimated to range from 5 to 40%<sup>66</sup> in contrast to the less than 2% observed with naloxone.<sup>67</sup> Therefore, when naltrexone is used in an AD opioid formulation, it needs to be sequestered so that it does not result in withdrawal symptoms in patients. Troxyca is thus formulated with barrier layers including a sequestering membrane intended to sequester the naltrexone.

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<sup>61</sup> In Troxyca naltrexone is present as its HCl salt form.

<sup>62</sup> NDA 207621, Troxyca Clinical Review at 19 (Sep. 14, 2015).

<sup>63</sup> Id.

<sup>64</sup> In contrast, naloxone differs from oxycodone in that the methyl group on the nitrogen atom is replaced by an allyl group.

<sup>65</sup> Upon approval, Revia received 5-year NCE exclusivity.

<sup>66</sup> Revia Labeling (revised Oct. 3, 2013), Clinical Pharmacology Section (Pharmacokinetics – Absorption).

<sup>67</sup> Id.

Specifically, Troxyca is formulated as a hard gelatin capsule filled with individual pellets containing rate-controlling excipients and oxycodone separated from the naltrexone inner core by a barrier layer.<sup>68</sup> If the intact capsule (or sprinkled pellets) is ingested orally, oxycodone is released with an extended-release profile to provide analgesia, while naltrexone largely remains sequestered. However, upon crushing or chewing the capsule or the pellets, naltrexone is released, resulting in antagonism of the pharmacodynamic effects of oxycodone, including drug liking and high.<sup>69</sup>

To support the approval of the Troxyca NDA, Pfizer conducted two Phase 3 efficacy and safety studies to assess whether sequestered naltrexone could potentially compromise the analgesic effects of oxycodone or safety due to systemic exposure of a small amount of naltrexone that escapes the inner core. Pfizer also conducted three human abuse liability studies to assess the AD properties of the formulation.<sup>70</sup>

### III. DISCUSSION

#### A. Three-Year Exclusivity for Targiniq Does Not Block Approval of the 505(b)(2) NDA for Troxyca

The issue addressed in this memorandum is whether the 3-year exclusivity for Targiniq, a fixed-combination containing the active moieties oxycodone and naloxone, will block the approval of the 505(b)(2) NDA for Troxyca, a fixed-combination containing the active moieties oxycodone and naltrexone. We conclude that it should not.

Targiniq is a fixed-combination that contains two active ingredients (oxycodone HCl and naloxone HCl), which contain oxycodone and naloxone as active moieties. In 2014, at the time of approval of the original NDA for Targiniq, FDA determined that no active ingredient (neither oxycodone HCl nor naloxone HCl) contained an active moiety that had not been previously approved, and thus no 5-year NCE exclusivity attached. FDA has since proceeded with determining eligibility for 3-year exclusivity and concluded that Targiniq has 3-year exclusivity. As explained in Section I.B. above, the conditions of approval of *such drug* necessarily encompass the particular combination of active moieties for which the application was submitted and for which new clinical investigations were essential. The conditions of approval for Targiniq are for the drug containing the combination of active moieties – oxycodone and naloxone. That exclusivity expires on July 23, 2017. Thus, the exclusivity-protected conditions of approval only bar approval of other 505(b)(2) NDAs for drugs containing the same combination of active moieties approved in Targiniq and that otherwise seek approval for the same exclusivity-protected conditions of approval as Targiniq. Because Troxyca does not

<sup>68</sup> Troxyca Clinical Review at 12-13. [REDACTED]

(b) (4)

<sup>69</sup> Troxyca Clinical Review at 12-13, 21. See also, NDA 207621, Troxyca CSS Review at 2 (Sep. 16, 2015).

<sup>70</sup> Troxyca Clinical Review at 22. Pfizer also conducted five pharmacodynamic studies to assess the dose ratio for oxycodone to naltrexone.

contain the same combination of active moieties approved in Targiniq, any approval of Troxyca is not an approval for the “conditions of approval of such drug in the approved subsection (b) application” for which Targiniq currently has exclusivity and no additional inquiry is required. Therefore, we recommend that the exclusivity awarded to Targiniq should not block approval of Troxyca.<sup>71</sup>

**B. The Board’s Recommendation that Targiniq’s 3-Year Exclusivity Should Not Block Approval of Troxyca Is Consistent with FDA Regulations, Congressional Intent, and the Targiniq Approval**

The Board’s recommendation that 3-year exclusivity for Targiniq should not block approval of Troxyca is consistent with the Agency’s regulations regarding fixed-combinations and with the approval of the Targiniq NDA. FDA regulations generally require that the combination as a whole be shown to be safe and effective and that each component (drug) in the fixed-combination be shown to contribute to efficacy.<sup>72</sup> Generally, it is not adequate for a sponsor to demonstrate only that the individual components are safe and effective. The regulation describes “special cases” (or examples) of the general rule regarding when a sponsor must demonstrate that each component (drug) in a combination contributes to the combination’s claimed effect. These examples include when a component is added to the combination: “(1) [t]o enhance the safety or effectiveness of the principal active component;” and “(2) [t]o minimize the potential for abuse of the principal active component.”<sup>73</sup>

Targiniq is one of these special cases. Targiniq was approved as a 505(b)(2) application that relied, in part, on a cross-reference to two applications for previously approved single-entity oxycodone products (original and reformulated OxyContin) and on the Agency’s finding of safety and effectiveness for a single-entity naloxone product (Narcan). For the initial approval of Targiniq, however, it was not sufficient for the sponsor to rely only on studies or findings of safety and efficacy for drugs containing the individual active moieties oxycodone and naloxone alone. Rather, the sponsor needed to conduct an adequate and well-controlled efficacy study to demonstrate that detectable levels of naloxone in systemic circulation do not interfere with analgesic efficacy.<sup>74</sup> Moreover, the sponsor needed to investigate how the presence of naloxone as the antagonist to oxycodone affects the AD properties of the combination product. Both components are therefore integral to the safety and effectiveness of Targiniq and it follows that the conditions of approval for Targiniq necessarily include the fact that it contains the combination of oxycodone and naloxone. This is consistent with FDA’s conclusion that the conditions of approval for Targiniq supported by new clinical investigations relate to the

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<sup>71</sup> If both Targiniq and Troxyca contained the same combination of the two active moieties oxycodone and naloxone, we would need to assess further the scope of exclusivity of Targiniq. We need not reach this aspect of the scope of inquiry here, however, because Targiniq and Troxyca do not contain the same combination of active moieties. Rather, Targiniq contains a combination of oxycodone and naloxone, a characteristic that distinguishes it from Troxyca, which contains oxycodone and naltrexone.

<sup>72</sup> See 21 CFR 300.50.

<sup>73</sup> 21 CFR 300.50(a)(2).

<sup>74</sup> Targiniq CDTL Review at 19, 30-35.

combination of active moieties; and, consequently, any 3-year exclusivity for Targiniq cannot block approval of a drug with a different combination of active moieties than Targiniq.<sup>75</sup>

Further, the Board's recommendation in this case is consistent with the goals of the Hatch-Waxman Amendments. The Board's interpretation of the 3-year exclusivity provisions is intended to encourage and reward innovation by protecting a fixed-combination for which new clinical investigations were essential to approval against approval of drugs with the same combination of active moieties for the same exclusivity-protected condition(s) of approval. The Board's interpretation ensures that 3-year exclusivity for a fixed-combination, if granted, does not block approval of different fixed-combinations (different combinations of active moieties) or of single-entity products. It also ensures that such exclusivity does not block approval of the same fixed-combination (the same combination of active moieties) for condition(s) of approval that were not supported by the new clinical investigations essential to approval. It therefore promotes and protects innovation while also encouraging the development of alternative therapies.

### **C. Targiniq's 3-Year Exclusivity Does Not Block the Approval of Fixed-Combinations of Oxycodone with Any Opioid Receptor Antagonist**

In a letter to the Agency dated September 18, 2015, Purdue claims that Targiniq's 3-year exclusivity blocks other solid oral dosage form oxycodone drug products with agonist/antagonist combination-based AD features, regardless of the specific opioid antagonist utilized and regardless of whether the products are labeled to describe their AD characteristics.<sup>76</sup>

Purdue asserts that Targiniq's AD properties are attributable to the presence of the opioid-receptor antagonist in the product, and the inability to readily separate this component from the agonist oxycodone.<sup>77</sup> As the first oxycodone/antagonist fixed-combination to be shown to have AD properties, Purdue claims that Targiniq confirms the viability of oxycodone/antagonist fixed-

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<sup>75</sup> The Board's recommendation here is consistent with the Agency's decisions on the approvals of NDA 206544 for MorphaBond (morphine sulfate) ER tablets, NDA 207932 for Belbuca (buprenorphine) buccal film, NDA 208411 for Narcan (naloxone) nasal spray, and NDA 204442 for Probuphine (buprenorphine) implant. The Agency determined that the Oct. 2, 2015, approval of the NDA for MorphaBond was not blocked by any unexpired 3-year exclusivity for Embeda (morphine sulfate and naltrexone) ER capsules (NDA 022321). The Agency also similarly determined that the Oct. 23, 2015, approval of the NDA for Belbuca was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone) or Zubsolv (buprenorphine and naloxone). The Agency also determined that the Nov. 18, 2015, approval of the NDA for Narcan nasal spray was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone), Targiniq (oxycodone and naloxone), or Zubsolv (buprenorphine and naloxone). The Agency determined that the May 26, 2016 approval of the NDA for Probuphine was not blocked by any unexpired 3-year exclusivity for Bunavail (buprenorphine and naloxone) or Zubsolv (buprenorphine and naloxone).

<sup>76</sup> Letter from Peter R. Mathers and Jennifer A. Davidson, Kleinfeld Kaplan & Becker, LLP on behalf of Purdue to Jay Sitlani, Office of Regulatory Policy, CDER, FDA and Kim Dettelbach, Office of Chief Counsel, FDA (Sep. 18, 2015) ("Purdue Letter") at 14. Purdue also argues that 3-year exclusivity for Targiniq blocks the approval of other fixed-combinations containing oxycodone and naloxone for the treatment of pain. *Id.* at 15-16. We need not address this argument in this memo, as Troxyca is a fixed-combination that contains the active moieties oxycodone and naltrexone.

<sup>77</sup> *Id.* at 14.

combinations for imparting meaningful AD properties.<sup>78</sup> Purdue thus concludes that exclusivity for this innovation should extend to all combinations of oxycodone with *any* opioid receptor antagonist.<sup>79</sup> Moreover, according to Purdue, Targiniq's status as the first agonist/antagonist oxycodone combination with recognized AD properties, and the related labeling statements about the AD attributes and their expected consequences, both separately constitute innovative conditions of approval for Targiniq.<sup>80</sup> Therefore, Purdue asserts that exclusivity extends to Targiniq's status as the first oxycodone product with agonist/antagonist combination-based AD features, and separately to the related labeling statements describing those features.<sup>81</sup> Under Purdue's proposed reading of Targiniq's exclusivity, final approval of products such as Troxyca could not be made effective until Targiniq's 3-year exclusivity period expires.

Purdue's assertions and arguments are inconsistent with the Agency's regulations and the Targiniq approval. As explained in Section III.A. and III.B., Targiniq's 3-year exclusivity for the conditions of approval of NDA 205777 is tied to the specific combination of its active moieties, oxycodone and naloxone, not merely the combination of oxycodone with *any* antagonist. The conditions of approval for which Targiniq received exclusivity necessarily encompass its particular combination of active moieties for which new clinical investigations were essential.<sup>82</sup>

#### IV. CONCLUSION

For all of these reasons, the Board recommends that the 3-year exclusivity for approval of NDA 205777 for Targiniq, which contains the two active moieties oxycodone and naloxone, should not block approval of Troxyca, which contains the two active moieties oxycodone and naltrexone.

DAAAP concurs with this recommendation.

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<sup>78</sup> Id.

<sup>79</sup> Id. Emphasis added.

<sup>80</sup> Id.

<sup>81</sup> Id. at 6-7.

<sup>82</sup> The Board's recommendation here that Targiniq's 3-year exclusivity does not block the approval of Troxyca turns on Targiniq and Troxyca having different combinations of active moieties. We therefore do not need to assess the second aspect of the scope inquiry as described in Section I.B. Under the second aspect of the scope inquiry, FDA would need to analyze the conditions of approval supported by the new clinical investigations essential to approval of Targiniq and whether Troxyca was otherwise seeking approval for the exclusivity-protected conditions of approval for Targiniq.

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/s/  
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DIANA L WALKER  
08/19/2016

SHARON H HERTZ  
08/19/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Drug Utilization Review**

Date: May 2, 2016

Reviewer: Joann H. Lee, Pharm.D.  
Drug Utilization Data Analyst  
Division of Epidemiology II (DEPI II)

Team Leader Rajdeep Gill, Pharm.D.  
Drug Utilization Data Analysis Team Leader  
DEPI II

Division Director LCDR Grace Chai, Pharm.D.  
For Drug Utilization DEPI II

Drug Name(s): Troxyca (oxycodone/naltrexone) Extended-Release (ER)

Application Type/Number: NDA 207621

Applicant/sponsor: Pfizer, Inc.

OSE RCM #: 2016-574

## CONTENTS

|  |   |
|--|---|
| EXECUTIVE SUMMARY.....                               | 2 |
| 1 INTRODUCTION .....                                 | 3 |
| 1.1 Background' .....                                | 3 |
| 1.2 Product Information.....                         | 3 |
| 2 METHODS and MATERIALS.....                         | 4 |
| 2.1 Determining Setting of Care.....                 | 4 |
| 2.2 Data Sources Used.....                           | 5 |
| 3 RESULTS .....                                      | 5 |
| 3.1 Prescription Data .....                          | 5 |
| 3.2 Prescriber Specialty for Oxycodone ER.....       | 6 |
| 4 DISCUSSION .....                                   | 6 |
| 5 CONCLUSION.....                                    | 7 |
| 6 APPENDICES .....                                   | 8 |
| 6.1 APPENDIX A: TABLES .....                         | 8 |
| 6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS ..... | 9 |

## **EXECUTIVE SUMMARY**

In preparation for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) scheduled for June 8, 2016, this review summarizes the drug utilization analyses of oxycodone ER and other extended-release/long-acting (ER/LA) opioid analgesics to provide context and background information.

The purpose of this Advisory Committee Meeting is to discuss whether the data submitted by the Sponsor for a new drug application of an opioid combination extended-release formulation (oxycodone/naltrexone ER) are sufficient to support labeling as a product with properties expected to deter abuse. The proposed indication of this new drug application is for the management of chronic pain that may require around the-clock, opioid treatment and for which alternative treatment options are inadequate.

This drug utilization review focused on the U.S. outpatient retail prescription utilization trends of oxycodone ER and all other ER/LA opioid analgesics from 2011 through 2015. During the examined time period, a decrease in utilization was observed in the number of prescriptions dispensed for oxycodone ER. The total number of prescriptions dispensed decreased by approximately 24% from 5.8 million prescriptions in 2011 to 4.4 million prescriptions in 2015. In contrast, some of the other ER/LA opioid analgesics (buprenorphine TD, tapentadol ER, hydrocodone ER, hydromorphone ER, and morphine ER) showed an overall uptake in utilization from 2011 through 2015 as most of these products were approved around or after 2010.

Our overall findings suggest that utilization of oxycodone ER declined from 2011 through 2015 and it was the third most frequently dispensed drug in the ER/LA opioid analgesic market during 2015, after morphine ER and fentanyl transdermal patch. The top physician specialties prescribing oxycodone ER was family practice/general practice/osteopathy in 2015.

## 1 INTRODUCTION

In preparation for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) scheduled for June 8, 2016, this review summarizes the drug utilization patterns of oxycodone ER and other extended-release/long-acting (ER/LA) opioid analgesics to provide context and background information. The purpose of this Advisory Committee Meeting is to discuss whether the data submitted by the Sponsor for a new drug application of an opioid combination product (oxycodone/naltrexone) are sufficient to support labeling as a product that may have abuse deterrent properties. The proposed indication is for the management of chronic pain that may require around the-clock, opioid treatment and for which alternative treatment options are inadequate.

### 1.1 BACKGROUND<sup>1,2</sup>

NDA 207621 was submitted by the Sponsor as the first extended-release combination product that contains *oxycodone hydrochloride and naltrexone hydrochloride* (Troxyca ER). Currently, there are two extended-release, analgesic combination drug product containing an opioid agonist and an opioid antagonist in the U.S. market, Embeda (morphine/naltrexone) and Targiniq (oxycodone/naloxone). The proposed indication of Troxyca ER under consideration is for the management of chronic pain that may require daily, around the-clock, opioid treatment and for which alternative treatment options are inadequate.<sup>3</sup>

This drug utilization review is provided as context for the discussions to be held at the upcoming Advisory Committee Meeting on June 8, 2016.

### 1.2 PRODUCT INFORMATION

Table 1 provides the list of all brand and generic drug products covered under the ER/LA opioid analgesic REMS program included in this review:

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<sup>1</sup> Oxycontin ER Prescribing Information accessed March-2016 at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/022272s0271bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s0271bl.pdf)

<sup>2</sup> Naltrexone hydrochloride Prescribing Information accessed March-2016 at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/75-434\\_Naltrexone%20Hydrochloride\\_prntlbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/75-434_Naltrexone%20Hydrochloride_prntlbl.pdf)

<sup>3</sup> PF-06412527 (ALO-02) Extended-Release Capsules/NDA 207621/Common Technical Document (CTD) Introduction:  
<http://darrrts.fda.gov:9602/darrrts/changeAppViewAppHistory.do?applicationId=207798&submissionHistoryFlag=0>  
Accessed April-2016

**Table 1. Oxycodone ER and all other opioid ER/LA opioid analgesic products<sup>4</sup>**

| Active Ingredient   | Trade Name                                 | Approval Date     |
|---|--|-------------------|
| Methadone tablets or liquid   | Dolophine                                  | March 14, 1973    |
| <b>Extended-release, Oral-dosage Forms Containing Active Ingredient</b>   |  |                   |
| Morphine ER   | MS Contin                                  | May 29, 1987      |
|   | Kadian                                     | July 3, 1996      |
|   | Avinza                                     | Feb 20, 2002      |
|   | Embeda (morphine/naltrexone)*              | Aug 13, 2009      |
|   | Morphabond**                               | October 2, 2015   |
| Oxycodone ER  | Oxycontin                                  | December 12, 1995 |
|   | Targiniq (oxycodone/naloxone) <sup>†</sup> | July 23, 2014     |
| Hydromorphone ER  | Exalgo                                     | March 1, 2010     |
| Oxymorphone ER  | Opana ER                                   | June 22, 2006     |
| Tapentadol ER   | Nucynta ER                                 | August 25, 2011   |
| Hydrocodone ER  | Zohydro ER                                 | October 25, 2013  |
|   | Hysingla ER                                | November 20, 2014 |
| <b>Transdermal Delivery Systems</b>   |  |                   |
| Fentanyl Transdermal  | Duragesic                                  | August 7, 1990    |
| Buprenorphine Transdermal   | Butrans                                    | June 30, 2010     |
| <p>*Embeda ER (morphine/naltrexone) was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.</p> <p>**Morphabond approved in October 2015, drug utilization data not available for this review.</p> <p><sup>†</sup>Targiniq ER (oxycodone/naloxone) is currently not marketed in the United States.</p> |  |                   |

## 2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review. (see Appendix B for full database description).

### 2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives™ was used to determine various retail and non-retail channels of distribution for the ER/LA opioid analgesics. The sales data for 2015 shows that

<sup>4</sup> Drugs at FDA: Approved Risk Evaluation and Mitigation Strategies (REMS) at <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisDetails.page&REMS=17>. Accessed March-2016.

approximately 75% of oxycodone ER bottles or packages were distributed to outpatient retail pharmacies (including chain, independent, and food stores). The sales data for all other ER/LA opioids (Table 1, Section 1.2) also show that majority of sales were towards retail pharmacies (including chain, independent, and food stores). Therefore, outpatient retail pharmacy utilization patterns were examined in this review for the opioid ER/LA analgesic products. Mail-order/specialty and non-retail settings were not included in this review.

## 2.2 DATA SOURCES USED

*The IMS, National Prescription Audit™ (NPA) database* was used to obtain nationally estimated number of prescriptions dispensed for oxycodone ER and all other ER/LA opioid analgesics (Table 1, Section 1.2) from U.S. outpatient retail pharmacies, from 2011 through 2015, annually.

NPA database was also used to obtain the nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies, stratified by top prescriber specialties for 2015.

## 3 RESULTS

### 3.1 PRESCRIPTION DATA

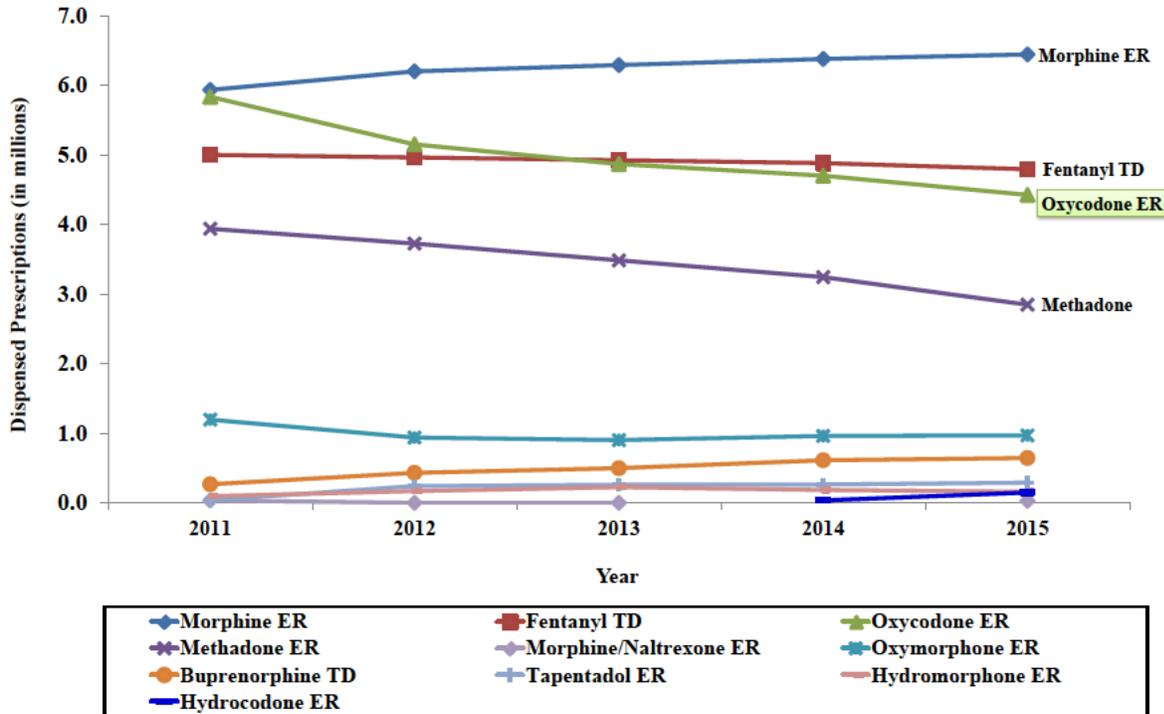
**Figure 1 below and Table 2 in Appendix A** show the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies from 2011 through 2015.

Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2011 through 2015. In 2015, morphine ER accounted for 31% (6.4 million prescriptions) of the total ER/LA prescriptions dispensed, followed by fentanyl TD (23%, 4.8 million prescriptions), and oxycodone ER (21%, 4.4 million prescriptions). Methadone prescriptions accounted for 14% (2.8 million prescriptions) of the total ER/LA prescriptions dispensed.

Looking at the yearly trends, oxycodone ER prescriptions dispensed decreased by 24% from 2011 through 2015. Morphine ER prescriptions dispensed increased by approximately 9% and fentanyl TD remained steady while prescriptions for methadone decreased by 28% from 2011 through 2015.

**FIGURE 1**

**Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies from 2011 - 2015**



Source: IMS, National Prescription Audits (NPA) Data extracted March 2015. File: NPA 2016-574 Rx Troxyca ERLA AC 04-04-16.xlsx  
\*\*No data for years 2011, 2012, and 2013 for hydrocodone products: Zohydro ER approved in 10/2013 and Hysingla ER approved 11/2014

### 3.2 PRESCRIBER SPECIALTY FOR OXYCODONE ER

Table 3 in Appendix A provides the total number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies by the top prescribing specialties for year 2015. Family practice/general practice/osteopathy was the top prescriber specialty (26% of total prescriptions) followed by internal medicine (12%), nurse practitioner (11%) and anesthesiology (11%) in 2015.

## 4 DISCUSSION

This review provides drug utilization data for oxycodone ER and other ER/LA opioid analgesics as context and background information in support of discussions for a new drug application for an extended-release formulation of an opioid combination product (oxycodone/naltrexone ER). During the examined time period, a decrease in utilization was observed in the number of prescriptions dispensed for oxycodone ER. The steady decline in the overall utilization of oxycodone ER may be attributed to multiple factors such as the introduction of reformulated OxyContin (oxycodone ER) to the market in August 2010, approval of other ER/LA opioid analgesics since year 2010, the ER/LA opioid analgesic REMS, federal and state level regulations in addition to other initiatives and actions by various organizations.

The prescription data showed that primary care providers such as family practice/internal medicine/osteopathy were the top prescriber specialties for oxycodone ER in 2015.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for 2015 showed that a vast majority of various ER/LA opioid bottles or packages were distributed to outpatient retail pharmacies. We focused our analysis on only the outpatient retail pharmacy settings; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. All changes over time or between products should be considered approximate and may be due to random error.

## **5 CONCLUSION**

Our overall findings suggest that utilization of oxycodone ER declined from 2011 through 2015 and was the third most frequently dispensed drug (4.4. million prescriptions dispensed) in the ER/LA opioid analgesic market during 2015, after morphine ER and fentanyl transdermal patch. Approximately one-quarter of oxycodone ER prescriptions were written by family practice/general practice/osteopathy in 2015.

## 6 APPENDICES

### 6.1 APPENDIX A: TABLES

**TABLE 2.**

**Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015**

|                        | 2011              |               | 2012              |               | 2013              |               | 2014              |               | 2015              |               |
|------------------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|
|                        | Prescriptions (N) | Share (%)     |
| <b>Grand Total</b>     | <b>22,330,862</b> | <b>100.0%</b> | <b>21,817,818</b> | <b>100.0%</b> | <b>21,446,002</b> | <b>100.0%</b> | <b>21,256,647</b> | <b>100.0%</b> | <b>20,742,630</b> | <b>100.0%</b> |
| Morphine ER            | 5,931,628         | 26.6%         | 6,198,303         | 28.4%         | 6,288,088         | 29.3%         | 6,375,570         | 30.0%         | 6,441,121         | 31.1%         |
| Fentanyl TD            | 4,997,384         | 22.4%         | 4,961,133         | 22.7%         | 4,923,139         | 23.0%         | 4,881,447         | 23.0%         | 4,791,686         | 23.1%         |
| <b>Oxycodone ER</b>    | <b>5,831,523</b>  | <b>26.1%</b>  | <b>5,148,631</b>  | <b>23.6%</b>  | <b>4,865,489</b>  | <b>22.7%</b>  | <b>4,699,154</b>  | <b>22.1%</b>  | <b>4,423,455</b>  | <b>21.3%</b>  |
| Methadone              | 3,938,607         | 17.6%         | 3,725,332         | 17.1%         | 3,484,537         | 16.2%         | 3,242,281         | 15.3%         | 2,846,882         | 13.7%         |
| Oxymorphone ER         | 1,196,953         | 5.4%          | 939,908           | 4.3%          | 901,305           | 4.2%          | 960,933           | 4.5%          | 968,029           | 4.7%          |
| Buprenorphine TD       | 266,332           | 1.2%          | 431,793           | 2.0%          | 497,697           | 2.3%          | 613,086           | 2.9%          | 643,634           | 3.1%          |
| Tapentadol ER          | 37,531            | 0.2%          | 242,059           | 1.1%          | 259,294           | 1.2%          | 264,048           | 1.2%          | 289,459           | 1.4%          |
| Hydromorphone ER       | 95,823            | 0.4%          | 170,654           | 0.8%          | 226,452           | 1.1%          | 185,035           | 0.9%          | 160,632           | 0.8%          |
| Hydrocodone ER         | —                 | —             | —                 | —             | —                 | —             | 35,093            | 0.2%          | 149,957           | 0.7%          |
| Morphine/Naltrexone ER | 35,081            | <1%           | 5                 | <0.1%         | 1                 | <0.1%         | —                 | —             | 27,775            | <1%           |

Source: IMS, National Prescription Audit (NPA). Extracted April 2016. File: NPA 2016-574 Rx Troxyca ERLA AC 04-22-16.xlsx

**TABLE 3.**

**Nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies, stratified by top 10 prescriber specialties, 2015**

| PRESCRIBER SPECIALTY                        | Prescriptions (N) | Share (%)     |
|---|-------------------|---------------|
| <b>Oxycodone ER Total Prescriptions</b>     | <b>4,423,455</b>  | <b>100.0%</b> |
| Family Practice/General Practice/Osteopathy | 1,161,703         | 26.3%         |
| Internal Medicine                           | 533,490           | 12.1%         |
| Nurse Practitioner                          | 506,116           | 11.4%         |
| Anesthesiology                              | 499,795           | 11.3%         |
| Physician Assistant                         | 425,805           | 9.6%          |
| Physical, Medicine & Rehabilitation         | 360,153           | 8.1%          |
| Pain Medicine                               | 216,042           | 4.9%          |
| Oncology                                    | 141,366           | 3.2%          |
| Orthopedic Surgery                          | 135,106           | 3.1%          |
| Neurology                                   | 81,408            | 1.8%          |
| All Other Specialties                       | 362,471           | 8.2%          |

Source: IMS, National Prescription Audit (NPA). Year 2015. Extracted April-2016. File: NPA 2016-572-specialty oxycodone ERLA AC.xlsx

## **6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS, National Prescription Audit**

The National Prescription Audit (NPATM) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPATM receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

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/s/  
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JOANN H LEE  
08/08/2016

RAJDEEP K GILL  
08/08/2016

GRACE CHAI  
08/09/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: April 27, 2016

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

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, CPH  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

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

Drug Name (established name): TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules, for oral use, CII

Dosage Form and Route:

Application Type/Number: 207621

Applicant: Pfizer, Inc.

## **1 INTRODUCTION**

On December 19, 2014, Pfizer Inc. submitted for the Agency's review a New Drug Application (NDA) 207621 for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules. A collaborative review of the TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules Medication Guide was completed on September 14, 2015 by the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP). Subsequently, a safety labeling change was issued for the class of extended-release/long-acting (ER/LA) opioid analgesic products. The Prescribing Information was updated to include a new Warning and Precaution (section 5.7 Adrenal Insufficiency) and Drug Interaction (section 7 serotonergic drugs) with corresponding information added to the Medication Guide.

The proposed indication for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) 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 focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on April 21, 2016 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules.

## **2 MATERIAL REVIEWED**

- Draft TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules MG and IFU received on December 19, 2014, and received by DMPP on April 20, 2016.
- Draft TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules Prescribing Information (PI) received on December 19, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on April 20, 2016.
- DMPP and OPDP Patient Labeling Review of TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules MG dated September 14, 2015.

## **3 REVIEW METHODS**

In our focused 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)

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG and IFU is appended to this memorandum. Consult DMPP 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.

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MORGAN A WALKER  
04/27/2016

BARBARA A FULLER  
04/27/2016

# Internal Consult

## \*\*\*\*Pre-decisional Agency Information\*\*\*\*

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

**To:** Joan Blair, Health Communications Analyst, DRISK

**From:** Koung Lee, Regulatory Review Officer, OPDP

**CC:** Jessica Fox, Regulatory Review Officer, OPDP  
Sam Skariah, Team Leader, 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:** December 15, 2015

**Re:** Extended-Release/Long-Acting (ER/LA) Opioid Products  
Comments on modified ER/LA Opioid SSS Risk Evaluation and Mitigation  
Strategies (REMS) Materials

---

### Materials Reviewed

OPDP has reviewed the following proposed SSS REMS materials for ER/LA opioid products:

- Healthcare Provider (HCP) REMS Materials:
  - Patient Counseling Document (PCD) on Extended Release/Long Acting Opioid Analgesics
  - FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
  - Prescriber Letter #3
  - ER/LA Opioid Analgesic REMS SSS website (screen shots for [www.ER-LA-opioidREMS.com](http://www.ER-LA-opioidREMS.com) )

The version of the draft REMS material used in this review, titled, “ERLA Opioid REMS Complete\_Clean\_Dec 2015.doc”, was sent from DRISK via email (Joan Blair, Health Communication Analyst) on Tuesday, December 8, 2015, and is attached to the end of this review.

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

### **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 following materials:

- Patient Counseling Document (PCD) on Extended Release/Long Acting Opioid Analgesics
- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Prescriber Letter #3
- ER/LA Opioid Analgesic REMS SSS website (screen shots for [www.ER-LA-opioidREMS.com](http://www.ER-LA-opioidREMS.com) )

OPDP notes that no changes were proposed for the Prescriber Letters #1 and #2 and the Professional Organization/Licensing Board Letters.

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

Thank you for your consult.

Enclosure:  
REMS Materials

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

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/s/  
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KOUNG U LEE  
12/15/2015



Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

### Division of Pediatric and Maternal Health Memorandum

**Date:** September 25, 2015      **Date consulted:** January 2, 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:** Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride extended release) capsules

**NDA:** 207621

**Applicant:** Pfizer, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** Analgesia for 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 2, 2015, DARRTS Reference ID 3681783
- Sponsor's submitted background package for NDA 207621, Troxyca ER
- DPMH review for Xartemis (NDA 204031), Leyla Sahin, MD, October 30, 2013.
- DPMH review for Targiniq (NDA 205777), Miriam Dinatale, D.O. June 20, 2014. DARRTS Reference ID 3526040.

- DPMH review for Zohydro ER (NDA 202880/S-003), Carol Kasten, MD. January 27, 2015, DARRTS Reference ID 3693127

### **Consult Question:**

DAAAP requests DPMH assistance with pregnancy and lactation labeling for this NDA.

### **INTRODUCTION**

On December 12, 2014, Pfizer, Inc submitted a 505 (b)(2) New Drug Application (NDA) for Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride extended release) capsules (NDA 207621) 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. The Referenced Listed Drugs (RLDs) are Revia (naltrexone hydrochloride), NDA 018932, and Roxicodone (oxycodone hydrochloride), NDA 021011.

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 Troxyca ER labeling with conversion to Pregnancy and Lactation Labeling Rule (PLLR) format.

### **BACKGROUND**

#### **Oxycodone**

Oxycodone is a semisynthetic opioid analgesic with affinity for mu, kappa, and delta receptors in the brain, spinal cord and peripheral organs.<sup>1</sup> 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.<sup>2</sup>

#### **Naltrexone**

Naltrexone is a centrally acting mu-opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding to mu-opioid receptors.<sup>3</sup> Naltrexone is used to treat opiate overdose, and in Troxyca ER, naltrexone is being used to prevent the abuse of oxycodone. When the capsule is tampered with for the purpose of abuse by intranasal or intravenous routes, rather than orally as intended, naltrexone is released and antagonizes the effects of oxycodone. However, in clinical trials with Troxyca ER, less than 2% of subjects in Phase 3 studies, experienced drug withdrawal symptoms despite taking an uncrushed and unchewed capsule, which suggests the potential for naltrexone exposure despite taking the medication as prescribed.

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<sup>1</sup> Dunnmon, Preston. DCRP Consult Review NDA 205777. 3/17/2014.

<sup>2</sup> Sahin, Leyla. PMHS-MHT Review- Xartemis XR (NDA 204031). 10/28/2013

<sup>3</sup> Drugs@FDA: Embeda (morphine sulfate and naltrexone hydrochloride) Extended Release capsules, section 12.1 Mechanism of Action, accessed 1/23/2015

### **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.<sup>4</sup> 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 therapy while pregnant). In addition to the boxed warnings, there is class labeling in several sections and sub-sections.<sup>5</sup>

### **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*,"<sup>6</sup> 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) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>7</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **REVIEW OF DATA**

### **Nonclinical Information**

In animal reproduction studies, there was no evidence of teratogenicity or embryofetal toxicity when oxycodone was orally administered to rats and rabbits at one and three times the adult human dose of 160mg/day, respectively, during the period of organogenesis. However, offspring of rats administered oxycodone during gestation were found to have neurobehavioral effects that included altered stress responses, hyperactivity, increased anxiety and altered learning and behavior. The reader is referred to the Nonclinical Review by Beth Bolan, Ph.D. for further details.

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<sup>4</sup> 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

<sup>5</sup> Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).

<sup>6</sup> Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

<sup>7</sup> 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).

## Oxycodone and Pregnancy

The applicant did not conduct studies with Troxyca ER (oxycodone HCl and naltrexone HCl) in pregnant women. However, there were a total of four cases of exposure to oxycodone HCl and naltrexone HCl (taken separately or in combination) during Phase 3 studies. Overall, there was one spontaneous abortion, one elective abortion, one normal delivery, and one questionable pregnancy. The data for these four cases is presented below. See appendix B for more details.

- *One spontaneous abortion (SAB):* 39 year old female treated with ALO-02 (oxycodone HCl combined with naltrexone) 80mg capsules twice daily. The patient was found to have a positive pregnancy test on study day 85. The patient went on to have a SAB on study day 116 (8-9 weeks gestation). There was no mention of any fetal abnormalities.
- *One elective abortion:* 19 year old female received two doses of intravenous (IV) naloxone (0.2mg and 0.6mg) during the Naloxone Challenge Phase and one day later had one dose of oxycodone HCl 20mg IV during the Drug Discrimination Phase. The day after the dose of oxycodone and two days after naloxone IV, the patient had a positive pregnancy test. The subject was discontinued from the study immediately and had induced abortion at four weeks gestation. There was no mention of any fetal abnormalities or the reason for the elective abortion.
- *One normal delivery:* 41 year old female treated with ALO-02 at a dose of 40mg daily for 100 days. She had a positive pregnancy test five days after discontinuation of the drug. The subject went on to deliver a healthy male infant who was full term (gestational age not given) who weighed 9 lb. 9 oz. There was no further information on this infant as the subject was unwilling to give this information to the study site.<sup>8</sup>
- *One questionable pregnancy:* 24 year old female was given two doses of IV naloxone (0.2mg and 0.6mg) as part of the naloxone challenge. During the Drug Discrimination Phase, the subject developed asymptomatic second degree atrioventricular block and was discontinued from the study. The subject was referred to a cardiologist for further work-up and mentioned to the cardiologist that she might be two months pregnant. There was no confirmation of pregnancy, and the subject refused to provide additional information.

### Oxycodone and Fetal Malformations

The applicant provided published literature regarding the use of oxycodone during pregnancy. DPMH reviewed the literature provided by the applicant and conducted its' own review of published literature to update the Pregnancy subsection of labeling for this application. Overall, there were three case-control studies that demonstrated statistically significant associations between opioid exposure in the first trimester of pregnancy and congenital malformations<sup>9,10,11</sup> and two studies that did not show an increase in congenital

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<sup>8</sup> Study B4531001-A Multicenter, 12-month, Open-Label, Single-Arm, Pfizer, Inc., October 23, 2014.

<sup>9</sup> Broussard C, Rasmussen S, Reefhuis J et al Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics Gynecology. 2011; 204: 314.

<sup>10</sup> Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional Use of Opioids and the Risk of Neural Tube Defects. Obstetrics and Gynecology. 2013 (122):4:838-844.

<sup>11</sup> Briggs, et al. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk, 7<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams and Wilkins: 2005: 378.

malformations.<sup>12,13</sup> These studies were reviewed by DPMH in 2013, and the reader is referred to the DPMH Review by Leyla Sahin, MD for further details.

#### *Reviewer's comments*

*Overall, the cumulative data on opioid exposure during pregnancy and congenital malformations are very limited. In an FDA Drug Safety Communication issued on January 9, 2015, FDA noted that they 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.<sup>14</sup>*

#### 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 the infant is not recognized early and does not get appropriate treatment. 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)<sup>15</sup> 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.<sup>16</sup>

#### **Oxycodone and Lactation**

The Drugs and Lactation Database (LactMed)<sup>17</sup> 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.” The applicant provided published literature regarding the use of oxycodone during lactation. DPMH reviewed the literature provided by applicant to update the Lactation subsection of labeling for this application. The studies are presented below.

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<sup>12</sup> Schick B, Hom M, Tolosa J, Librizzi R, Donnenfeld A. A preliminary analysis of first trimester exposure to oxycodone and hydrocodone. *Reprod Toxicol.* 1996;10:162.

<sup>13</sup> Heinonen OP, Slone D, Shapiro S. Analgesics and antipyretic drugs. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group Inc; 1977. p. 286–95.

<sup>14</sup> FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy. January 9, 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm>

<sup>15</sup> Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).

<sup>16</sup> 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

<sup>17</sup> <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.

In a lactation study (Marx, *et al.*), six post-cesarean section breastfeeding mothers were taking 1 to 2 capsules containing a combination of 5 mg oxycodone and 500 mg acetaminophen every 4 to 7 hours for post-cesarean section pain. Maternal plasma and colostrum samples were obtained prior to and 0.25, 0.5, 1, 1.5, 2 and 3 hours after the initial dose and prior to and 2 hours after each successive dose and 4, 8, and 12 hours after the final dose. Peak oxycodone milk levels occurred 1 to 2 hours after the first dose and then at variable times after successive doses. Oxycodone could be measured in milk up to 4, 12, and 36 hours after 4, 9, and 11 doses respectively. Oxycodone milk levels ranged from undetectable (<5 mcg/L) to 229 mcg/L. The authors estimated that an exclusively breastfed neonate would receive a maximum 8% of the maternal weight-adjusted dosage of oxycodone.<sup>18</sup>

*Reviewer comments:*

*In this study, the active metabolites of oxycodone (noroxycodone and oxymorphone) were not measured. Oxycodone has an oral bioavailability of 60% to 87% in adults. Noroxycodone is the major circulating metabolite with an area under the curve (AUC) of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations.<sup>19</sup> In addition, the estimated infant exposure was 8% of the maternal weight-adjusted dosage of oxycodone, which could lead to adverse events in exposed infants. Since the study did not measure the levels of the active metabolites, the relative infant dose of oxycodone plus its' active metabolites may have been even higher than 8%. Also, only colostrum was analyzed, which may not provide an accurate measure of drug in mature milk.*

In another lactation study (Seaton, *et al.*), 50 breastfeeding mothers, who delivered by cesarean section, received oxycodone for post-operative pain. Maternal plasma and colostrum samples were analyzed for oxycodone at 24 hour intervals (24, 48 and 72 hours postpartum without respect to the time of the previous oxycodone dose). The most common doses received by the mothers during the previous 24 hours were 60 mg, 40 mg, and 20 mg. Mean colostrum concentrations at the 3 collection times were 58 mcg/L (range 7 to 130 mcg/L), 49 mcg/L (range 0 to 168 mcg/L), and 35 mcg/L (range 0 to 31 mcg/L), respectively. Colostrum concentrations were 3.2 to 3.4 times higher than maternal serum levels. Five women had detectable oxycodone in milk 37 hours after the last dose. Forty-one infants had 45 blood samples taken at 48 hours. Only one of the samples had a detectable (>2 mcg/L) oxycodone level of 7.4 mcg/L. Less than 4% of neonates had an average sedation score<sup>20</sup> (over 48 hours) of 3, with no infants greater than 3. Sedation scores could not be correlated to maternal dose or to breast milk levels. The authors concluded that maternal oxycodone intake up to 72 hours post-cesarean section poses only a minimal risk to the breastfeeding infant since low volumes of breast milk are ingested during the first few days of life.<sup>21</sup>

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<sup>18</sup> Marx CM, Pucino F, Carlson JD et al. Oxycodone excretion in human milk in the puerperium. *Drug Intell Clin Pharm.* 1986;20:474

<sup>19</sup> [www.drugs.com/pro/oxycodone.html](http://www.drugs.com/pro/oxycodone.html)

<sup>20</sup> Sedation score: ranges from 1 (fully alert) to 5 (difficult to arouse)

<sup>21</sup> Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: Relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol.* 2007; 47:181-5.

*Reviewer comments*

*The concentrations of oxycodone in colostrum were 3.2 to 3.4 higher than maternal serum levels. This may be due to oxycodone accumulating in the breastmilk and having a different rate of clearance from the maternal plasma. Oxycodone was detectable in the breastmilk of five women 37 hours after the last dose. However, the study did not analyze the milk samples at peak times (1-2 hours post-dose). This may have caused underestimation of peak drug level in breastmilk.*

A retrospective cohort study (Lam, *et al.*), consisting of three cohorts (breastfeeding mother-infant pairs exposed to oxycodone (n=289), codeine (n= 681) or acetaminophen only (n=590)) was conducted, and the rate of central nervous system (CNS) depression in breastfeeding infants was compared. Of the 1560 files of women that were obtained, only 533 women were able to follow-up (139 in the oxycodone cohort, 210 in the codeine cohort and 184 in the acetaminophen cohort). Nursing mothers were contacted by telephone to determine the degree of maternally perceived CNS depression in their infants. In the oxycodone cohort, 20% of the mothers reported signs of CNS depression in their infants, compared to 16.7% in the codeine cohort and 0.5% in the acetaminophen cohort. The authors concluded that maternal use of oxycodone is associated with an increased risk of CNS depression in the breastfed infant.<sup>22</sup>

Several case reports have reported CNS depression in breast-fed infants of mothers taking oxycodone. In one case report (Timm, *et al.*), a breastfeeding 4-day old infant is brought to the emergency room with concerns for lethargy and poor feeding. The infant was born full-term via cesarean section; the mother had an uncomplicated pregnancy, and she and her infant were discharged home at 48 hours after delivery. The mother was sent home on Percocet (oxycodone 5mg with acetaminophen 325mg). The infant was exclusively breastfed and found to be well by his physician at 4 days postpartum. Later on the same day, the infant became sedated, became difficult to arouse and did not feed from either breast. The infant was brought to the emergency department where the infant was found to have lethargy, hypothermia, pinpoint pupils, and a poor sucking reflex. The mother reported that her milk had come in the previous evening. She had taken 10 mg of oxycodone that evening and another 5 mg the next morning in the form of Percocet. The infant was given naloxone 0.34 mg intramuscularly and within 2 minutes, the baby's eyes opened and he drank 45 mL of formula. No further sedation was seen over the next 24 hours. The reporting physician concluded that the infant's opioid intoxication was caused by oxycodone in breastmilk.<sup>23</sup>

*Reviewer comments:*

*The retrospective cohort study and several case studies have reported that CNS depression has been observed in infants exposed to oxycodone via breastmilk.*

There are no published studies looking at the effect of oxycodone on lactation and milk production in humans. Overall, the applicant noted that oxycodone has been detected in

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<sup>22</sup> Lam J, et al. Central nervous system depression of neonates breastfed by Mothers receiving oxycodone for postpartum analgesia. J Pediatr. 2012;160:33-37.e2.20

<sup>23</sup> Timm NL. Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. J Pediatr.2013; 162: 421-2.

human breast milk. Although there are case reports that show that oxycodone exposure may produce CNS depression, CNS depression was not consistently observed across all studies.<sup>24</sup>

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.<sup>25</sup>

### **Discussion**

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.<sup>26</sup> DPMH agrees with the applicant that breastfeeding is not recommended with Troxyca ER and will maintain consistency with other ER/LA opioids regarding the lactation section of labeling.

### **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.”

In a retrospective cohort study (Rubinstein, *et al.*), 81 men between the ages of 26 and 79 were treated with an opioid (buprenorphine (n=8), fentanyl (n=4), methadone (n=14), morphine CR (n=12), oxycodone (n=8), oxycodone IR (n=10), hydrocodone (n=25)) for chronic pain (low back pain, spinal stenosis, chronic headaches, peripheral neuropathy, rheumatoid arthritis) for at least three months. None of the men had a diagnosis of hypogonadism before opioid treatment. Total serum AM testosterone levels were measured, and 46 patients (56.8%) had hypogonadism (AM testosterone <250ng/dL) and 35 patients (43.2%) had normal testosterone levels. Seventy-four percent of men (34/46 males) who were receiving long-acting opioids had hypogonadism compared to 34% of men using short-acting opioids (12/35 men).<sup>27</sup>

### **Discussion**

Male hypogonadism is characterized by low serum testosterone (<300 ng/dL) in combination with at least one clinical sign or symptom. Signs of hypogonadism include absence or regression of secondary sex characteristics, anemia, muscle wasting, reduced bone mass, oligospermia, and abdominal adiposity. Symptoms of post-pubescent

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<sup>24</sup> Pfizer, Inc. Summary of Clinical Safety. NDA 207621. December 10, 2014.

<sup>25</sup> Sachs HC. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on selected topics. *Pediatrics* 2013; 132(3).

<sup>26</sup> Oxycodone HCl, ANDA 76168. Drugs@ FDA. Nursing Mothers section of labeling. Accessed 9/15/2015.

<sup>27</sup> Rubinstein, et al. Hypogonadism in men with chronic pain linked to the use of long-acting rather than short-acting opioids. *Clin J Pain*. 2013; 29 (10): 840-845.

hypogonadism include sexual dysfunction (erectile dysfunction, reduced libido, difficulty with orgasm, reduced ejaculate), reduced energy, depressed mood, increased irritability, difficulty concentrating.<sup>28</sup> Therefore, hypogonadism does not always translate to a decrease in fertility. Given the limitations in the study above (small sample size and inability to determine whether there was decreased fertility), DPMH does not recommend changes to labeling regarding infertility at this time.

### **Naltrexone and Pregnancy**

The applicant provided published literature regarding the use of naltrexone during pregnancy. Overall, there were several case reports and case series and one observational study of women who had been treated with naltrexone implants throughout pregnancy, and no negative outcomes have been observed for either the mothers or the infants.<sup>29,30,31, 32, 33</sup> Current naltrexone labeling states that adequate and well-controlled studies with naltrexone have not performed in pregnant women and to use the drug if the potential benefit justifies the risk.<sup>34</sup>

In adults, most of the naltrexone component of Troxyca ER will become inactive after oral administration of the drug. In Troxyca ER clinical trials, <2% of adult subjects exposed to Troxyca ER experienced symptoms of opioid withdrawal. Because the fetus may have an immature blood-brain barrier and because of reports of opioid withdrawal symptoms in adults in clinical trials with Troxyca ER, there is the potential that naltrexone may cause withdrawal symptoms in a fetus. Troxyca ER labeling will be placed in the PLLR format and Pregnancy, section 8.1, will state the following:

“Because plasma naltrexone levels were detectable in some patients administered TROXYCA ER in the clinical trials, the naltrexone component of TROXYCA ER may precipitate withdrawal in a fetus due to the immaturity of the fetal blood-brain barrier.”

### **Naltrexone and Lactation**

The Drugs and Lactation Database (LactMed)<sup>35</sup> was searched for available lactation data on the use of naltrexone. Limited data indicates that naltrexone is minimally excreted into

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<sup>28</sup> Kumar, et al. Male hypogonadism: Symptoms and treatment. *Journal of Advance Pharmaceutical Technology & Research*. 2010. 1 (3): 297-301.

<sup>29</sup> Hulse, et al. Naltrexone implant and blood naltrexone levels over pregnancy. *Australian and New Zealand Journal of Obstetrics and Gynecology*. 2003; 43: 386-388.

<sup>30</sup> Hulse, G, O'Neill, G, Arnold-Reed, D. Methadone maintenance vs. implantable naltrexone treatment in the pregnant heroin user. *International Journal of Gynecology and Obstetrics*. 2004; 85: 170-171.

<sup>31</sup> Hulse, et al. A possible role for implantable naltrexone in the management of the pregnant heroine user. *Australian and New Zealand Journal of Obstetrics and Gynecology*. 2002: 42(1): 93-94.

<sup>32</sup> Hulse, et al. Using naltrexone in the management of the pregnant heroine user. *Australian and New Zealand Journal of Obstetrics and Gynecology*. 2002: 42(5): 569-573.

<sup>33</sup> Hulse, et al. Obstetric and neonatal outcomes associated with maternal naltrexone exposure. *Australian and New Zealand Journal of Obstetrics and Gynecology*. 2001. 41 (4): 424-428.

<sup>34</sup> Vivitrol (naltrexone), NDA 21897. *Drugs@FDA*. Accessed 9/15/2015.

<sup>35</sup> <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

breastmilk. In Hale's Medication and Mother's Milk: A Manual of Lactational Pharmacology, Dr. Thomas Hale, a breastfeeding expert, classifies breastfeeding as moderately safe with maternal use of naltrexone.<sup>36</sup> The applicant provided one article regarding the use of naltrexone during lactation. The case report is reviewed below.

In a case report (Chan, *et al*), a 30 year old lactating opiate addict was undergoing oral naltrexone pharmacotherapy. The woman was 1.5 months postpartum and was taking 50mg of naltrexone daily. The woman's breast milk was sampled several times between 3.7 and 23 hours after her last dose of naltrexone. Naltrexone levels were undetectable by 8 hours after the dose (averaged 1.7 mcg/L) while the beta-naltrexol (active metabolite of naltrexone) milk levels remained detectable throughout the study period and averaged 46 mcg/L. The milk/plasma ratios of naltrexone and 6-beta-naltrexol were 1.9 and 3.4, respectively. The infant had detectable plasma levels of only beta-naltrexol at a low concentration of 1.1 mcg/L at 9.5 hours after the maternal dose, 30 minutes after starting a feeding. Naltrexone was undetectable in the infants' plasma. The infant was reported to be healthy with no adverse effects noted. The authors noted that an exclusively breastfed infant would receive 7mcg/kg of naltrexone daily, including the active metabolite, equivalent to 0.86% of the maternal weight-adjusted dosage.<sup>37</sup>

There are no human data on the effect of naltrexone on lactation. In addition, there are no animal data looking at the effect of naltrexone on lactation.

### **Discussion**

In adults, most of the naltrexone component of Troxyca ER will be inactivated following oral administration. If a small amount of naltrexone is transferred from the breast milk to the infant, there is a chance that naltrexone will be orally absorbed by the infant causing withdrawal symptoms. Although LactMed classifies breastfeeding as moderately safe with maternal use of naltrexone, this classification was based on the use of the product in an overdose situation, not on the potential daily, around-the-clock maternal use as would be the case with the use of this product. The "Nursing Mother" section of current naltrexone labeling states that "because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother."<sup>38</sup> DPMH recommends that Troxyca ER not be used in a breastfeeding mother and recommends the addition of the following phrase to "Clinical Considerations" subsection of section 8.2, Lactation:  
" (b) (4) may precipitate opioid withdrawal in a breastfed infant."

### **CONCLUSIONS**

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

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with breastfeeding.

<sup>36</sup> Hale, Thomas. Medications and Mother's Milk: A Manual of Lactational Pharmacology, 15<sup>th</sup> edition. Hale Publishing, L.P. 2012

<sup>37</sup> Chan, *et al*. Transfer of naltrexone and its metabolite 6, beta-naltrexol into human milk. J Hum Lact. 2004; 20 (3): 322-6.

<sup>38</sup> Vivitrol (naltrexone), NDA 21897. Drugs@FDA. Accessed 9/15/2015.

- **Warnings and Precautions, Section 5.3**
  - Based on the increased likelihood of adverse infant effects due clinical experience with oxycodone in pregnant women, a subsection describing embryo- and/or fetal risks (“Neonatal Opioid Withdrawal Syndrome”) as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).
- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of Troxyca ER labeling was formatted in the PLLR format to include “Risk Summary,” “Clinical Considerations,” and “Data” subsections.<sup>39</sup>
- **Lactation, Section 8.2**
  - The “Lactation” subsection of Troxyca ER labeling was formatted in the PLLR format to include the “Risk Summary” and “Clinical Considerations” subsections.<sup>40</sup>
- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of Troxyca ER labeling was updated to correspond with changes made to sections 5.3, 8.1, 8.2 and 8.3 of labeling.

## **RECOMMENDATIONS**

DPMH revised subsections 8.1, 8.2 and 17 in Troxyca 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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<sup>39</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

<sup>40</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

## DPMH Proposed Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) Labeling

### HIGHLIGHTS OF PRESCRIBING INFORMATION

#### **WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME**

Prolonged use of TROXYCA ER A during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening if not recognized and treated. If [REDACTED] (b) (4) 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 [REDACTED] (b) (4) use of TROXYCA 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 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 [see *Warnings and Precautions* (5.3)].

## 5 WARNINGS AND PRECAUTIONS

### 5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of TROXYCA ER during pregnancy can result in withdrawal [REDACTED] (b) (4) 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. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

## 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 TROXYCA ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Because plasma naltrexone levels were detectable in some patients

administered TROXYCA ER in the clinical trials, the naltrexone component of TROXYCA ER may precipitate withdrawal in a fetus due to the immaturity of the fetal blood-brain barrier [see *Clinical Pharmacology (12.3)*]. Animal reproduction studies with oral administration of oxycodone HCl in rats and rabbits during the period of organogenesis at doses equal to or 3-times, respectively, the human dose of 160 mg/day did not reveal evidence of teratogenicity or embryo-fetal toxicity. In several published studies, treatment of pregnant rats with oxycodone 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. (b) (4)

#### *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. TROXYCA ER is not recommended for use in pregnant women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including TROXYCA ER, can prolong labor through actions that 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*

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up to 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 1- and 3- times an adult human dose of 160 mg/day, respectively, on a mg/m<sup>2</sup> basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects including altered stress responses, 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 dose of 160 mg/day, on a mg/m<sup>2</sup> basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; equivalent to an adult human dose of 160 mg/day, on a mg/m<sup>2</sup> 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 breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended –release oxycodone, including TROXYCA ER, and no information is available on the effects of the drug on the breastfed 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 breastfed infant, advise patients that breastfeeding is not recommended during treatment with TROXYCA ER.

### Clinical considerations

(b) (4)  
Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped. Furthermore, naltrexone may precipitate opioid withdrawal in a breastfed infant.

## 17 PATIENT COUNSELING INFORMATION

### **Neonatal Opioid Withdrawal Syndrome**

Inform female patients of reproductive potential that prolonged use of TROXYCA 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)*, *Use in Specific Populations (8.1)*].

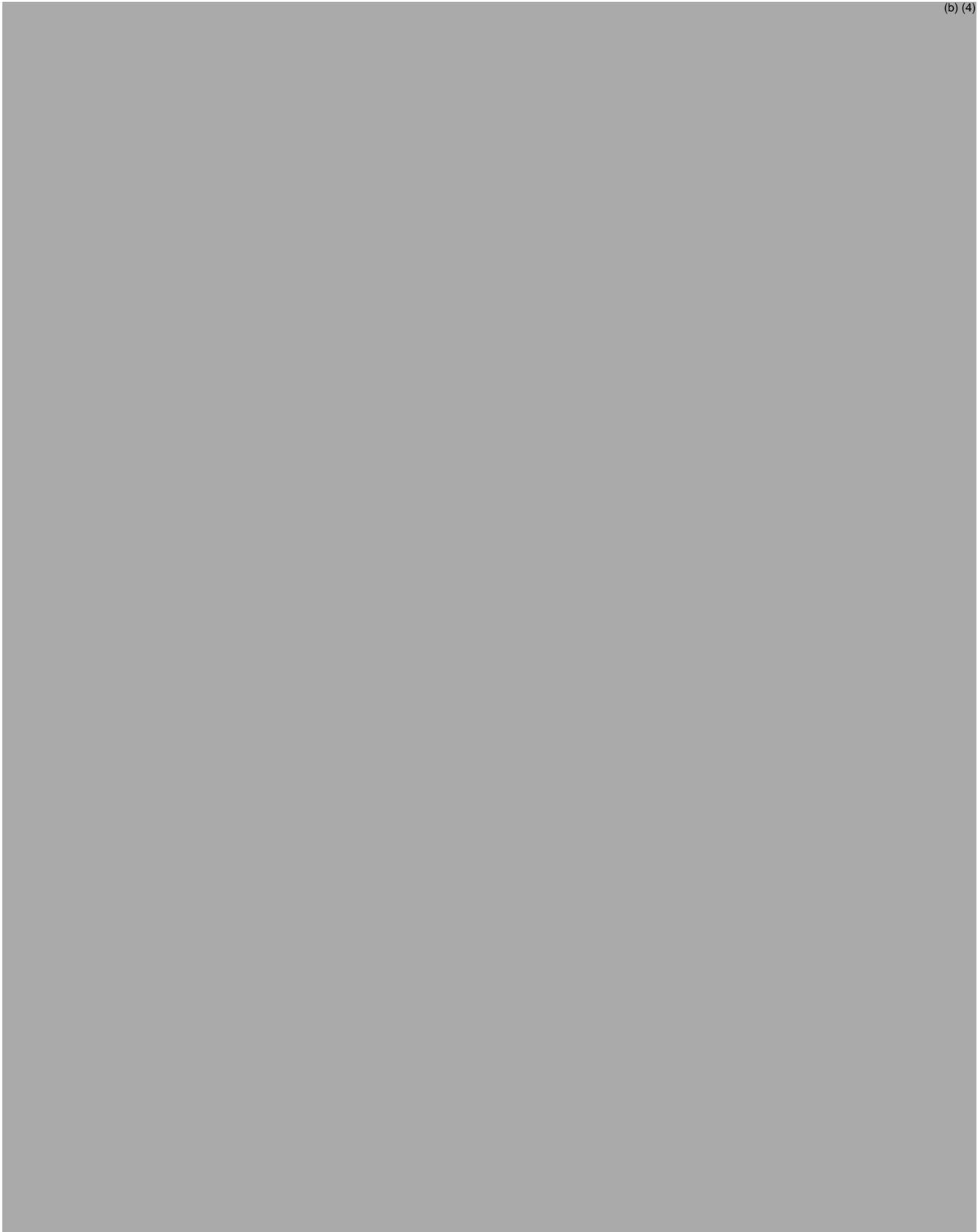
(b) (4)  
(b) (4) that TROXYCA ER can cause fetal harm and to inform their healthcare provider (b) (4) a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

### **Lactation:**

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

**APPENDIX A – Applicant’s Proposed Pregnancy and Nursing Mothers Labeling**

(b) (4)



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

## APPENDIX B: Pregnancy cases during Pfizer's Phase III Clinical Trials

- *One spontaneous abortion (SAB):* 39 year old female with a history of chronic low back pain was treated with oxycodone HCl and naltrexone HCl at 20mg daily and titrated up to 80mg daily by study day 22. The patient was on medroxyprogesterone acetate injections for contraception but did not receive contraception at the correct time. The patient was found to have a positive pregnancy test on study day 85. The patient went on to have a SAB on study day 116 (8-9 weeks gestation). There was no mention of any fetal abnormalities.
- *One elective abortion:* 19 year old female completed the Naloxone Challenge Phase and had one dose of oxycodone HCl 20mg IV during the Drug Discrimination Phase. The subject was discontinued from the study for not meeting protocol-specified randomization criteria #3.<sup>41</sup> The day after the dose of oxycodone and two days after naloxone IV, the patient had a positive pregnancy test. The subject went on to have an induced abortion at four weeks gestation. There was no mention of any fetal abnormalities and no reason for the elective abortion.
- *One normal delivery:* 41 year old female with a history of moderate to severe chronic non-cancer pain was treated with oxycodone HCl and naltrexone HCl. She was started on 30mg daily and then increased to 40mg once daily for a total of 100 days. The drug was discontinued after 100 days; five days after discontinuation of the drug, a pregnancy test was positive. The subject went on to deliver a healthy male infant who was full term (gestational age not given) who weighed 9 lb. 9 oz. The infant was normal and had no health problems. Attempts to contact the subject to acquire more information about the infant have been unsuccessful as the subject was unwilling to give this information to the study site.<sup>42</sup>
- *One questionable pregnancy:* 24 year old female enrolled in the randomized, double-blind, double-dummy, placebo and active-controlled, 6-way crossover study to determine abuse potential of oxycodone HCl and naltrexone HCl compared to oxycodone immediate-release and placebo. The subject had a history of recreational drug use in the 12 months before the screening. The patient was given two doses of naloxone HCl intravenously (IV) as part of the naloxone challenge. During the Drug Discrimination Phase, the subject developed asymptomatic second degree atrioventricular block and was discontinued from the study. The subject was referred to a cardiologist for further work-up and mentioned to the cardiologist that she might be two months pregnant. There was no confirmation of pregnancy, and the subject refused to provide additional information.

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<sup>41</sup> Criteria #3: tolerate study treatments safely: SpO<sub>2</sub> = 90% at 30 minutes post-dose)

<sup>42</sup> Study B4531001-A Multicenter, 12-month, Open-Label, Single-Arm, Pfizer, Inc., October 23, 2014.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MIRIAM C DINATALE  
09/25/2015

TAMARA N JOHNSON  
09/25/2015

LYNNE P YAO  
09/29/2015

MEMORANDUM

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



**Date:** September 16, 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:** ALO-02 (Oxycodone HCl-Naltrexone HCl ER Capsules), NDA 207-621  
Troxyca ER Capsules are for oral administration at dosage strengths (oxycodone HCl/naltrexone HCl) of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg  
**IND Number:** 107,037 (b) (4)  
**Indication(s):** Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.  
**Sponsor:** Pfizer Inc  
**PDUFA Goal Date:** October 19, 2015

**Materials Reviewed:**

In vitro physical manipulation and chemical extraction studies as well as three human abuse potential studies (B4981002, B4531008, and B4531009) submitted in support of NDA 207-621.

Table of Contents

I. Summary .....2

    1. Background.....2

    2. Conclusions.....2

    3. Recommendations.....6

II. Discussion.....6

    1. Chemistry.....6

        1.1 Substance information.....6

        1.3 In vitro manipulation and extraction studies for products with Abuse-Deterrent features .....8

|  |    |
|--|----|
| 4. Clinical Studies .....  | 17 |
| 4.1 Human abuse potential studies .....                              | 17 |
| 4.2 Adverse event profile through all phases of development .....    | 37 |
| 4.4 Evidence of abuse, misuse and diversion in clinical trials ..... | 37 |
| 5. Regulatory issues and assessment .....                            | 38 |
| 6. Other relevant information .....                                  | 39 |

## I. Summary

### 1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate from a CSS perspective NDA 207-621, submitted by Pfizer Inc., on December 19, 2014, for Troxyca ER Capsules (oxycodone HCl-naltrexone HCl ER Capsules). Troxyca ER Capsules are for oral administration at dosage strengths (oxycodone HCl/naltrexone HCl) of 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg.

The Agency approved the proprietary name of Troxyca ER Capsules (DARRTS, NDA 207621, March 11, 2015, Author: Vaishali Jarrel). This product was developed under INDs 107,037 (b) (4). It has not previously been marketed in any countries. Due to the presence of oxycodone, Troxyca ER Capsules will be in Schedule II of the Federal Controlled Substances Act.

### 2. Conclusions

1. Based on the cumulative data submitted by Sponsor, Troxyca ER Capsules when crushed provide a deterrent effect to abuse by oral, intranasal, and intravenous routes of abuse. Results from the three human abuse potential studies (B34531008, B4531009, and B4981002) demonstrate that administration of crushed Troxyca ER capsules via oral, intranasal, or intravenous routes of administration results in statistically, significantly lower levels of Drug Liking and High compared to administration of the positive control crushed IR oxycodone by corresponding routes of administration. The suppression of Drug Liking and High produced by crushed Troxyca ER capsules appears to be due to the antagonism by naltrexone of oxycodone-induced subjective effects including Drug Liking and High.
  - a. In oral human abuse potential study B4531008, maximum Drug Liking <sup>1</sup>(E<sub>max</sub>) produced by oral administration of crushed Troxyca ER pellets at doses of 40 mg/4.8 mg (E<sub>max</sub> =70.1 mm) and 60 mg/7.2 mg (E<sub>max</sub> = 74.4 mm) was significantly greater than that produced by placebo

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<sup>1</sup> Drug liking was measured using a 100 points bipolar Drug Liking scale (0= maximum disliking, 50= neutral, 100 maximum liking).

( $E_{\max} = 51.6$  mm) but significantly lower than that produced by either crushed oxycodone IR 40 mg ( $E_{\max} = 85.5$  mm) or crushed oxycodone IR 60 mg ( $E_{\max} = 89.7$  mm). Likewise, with respect to maximum High<sup>2</sup>, oral administration of crushed Troxyca ER pellets at doses of 40 mg/4.8 mg ( $E_{\max} = 47.3$  mm) and 60 mg/7.2 mg ( $E_{\max} = 53.4$  mm) was significantly greater than that produced by placebo ( $E_{\max} = 10.9$  mm) but significantly lower than that produced by either crushed oxycodone IR 40 mg ( $E_{\max} = 77.9$  mm) or crushed oxycodone IR 60 mg ( $E_{\max} = 84.7$  mm). These data suggest that orally administered crushed Troxyca ER Capsules is associated with some abuse potential that is significantly lower than that associated with orally administered crushed oxycodone IR tablets. The lower scores for  $E_{\max}$  of Drug Liking and High associated with crushed Troxyca ER compared to crushed oxycodone IR treatments, at similar doses, was not due to differences in bioavailability of oxycodone since corresponding treatments resulted in similar maximum oxycodone plasma levels ( $C_{\max}$ ), median times to reach  $C_{\max}$  ( $T_{\max}$ ), and areas under the oxycodone plasma concentration curve from 0 to 2 hours ( $AUC_{0-2hrs}$ ). This suggests that the differences result from the antagonism by naltrexone of oxycodone induced Drug Liking and High. (See Tables 7, 8 and 9 under Discussion)

- b. In intranasal (IN) human abuse potential study B4531009, crushed Troxyca ER 30 mg IN produced  $E_{\max}$  values for Drug Liking (60.5 mm) and High (26.6 mm) that were significantly lower than that produced by oxycodone IR 30 mg IN (92.8 mm for Drug Liking, 85.8 mm for High) but statistically similar to that of placebo (50.9 mm for Drug Liking and 2.2 mm for High). These data indicate little Drug Liking or High associated with crushed Troxyca ER 30 mg given intranasally. The data support a possible deterrent effect of Troxyca ER Capsules to intranasal abuse. (See Tables 11, 12 and 13 in Discussion)
- c. Data from simulated intravenous study B4981002 indicate that I.V. 2.4 mg naltrexone HCl can block the Drug Liking response and most of the High response produced by intravenous 20 mg oxycodone HCl. Simulated Troxyca ER 20 mg/2.4 mg injected intravenously produced  $E_{\max}$  for Drug Liking and High of 58.2 mm 17.4 mm, respectively, which were similar to that produced by intravenous placebo (52.3 mm for Drug Liking and 3.7 mm for High). By contrast, intravenous injection of oxycodone HCl 20 mg produced an  $E_{\max}$  of Drug Liking (92.4 mm) and High 93.1 mm that was statistically significantly greater than that produced by intravenous simulated Troxyca ER 20 mg/2.4 mg. For both active treatments, the concentration of oxycodone in plasma at 5 minutes post-dosing ( $C_{5min}$ ) and the various partial areas under the oxycodone concentration versus time curve (partial AUC) were similar; therefore, the differences in Drug Liking and High were not due to differences in oxycodone exposure. The 2.4 mg naltrexone HCl and 20 mg oxycodone HCl represents a (b) (4) ratio. The data suggest that in the event that Troxyca ER capsule contents are crushed, resulting in release of all the naltrexone, the preparation of a solution for intravenous injection using the crushed Troxyca ER capsule contents will not be effective in producing subjective effects such as Drug Liking or High. Troxyca ER capsules may have a deterrent effect to intravenous abuse when the capsule contents are crushed, due to the ability

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<sup>2</sup> High was measured using a 100 point unipolar scale where 100 represents maximum high

of the released naltrexone to block the effects of the concomitantly released oxycodone. (See Tables 15, 16, and 17 in the Discussion).

- d. What study B4981002 does not do is to establish the degree of blocking oxycodone HCl Drug Liking and High when the ratio of oxycodone HCl to naltrexone HCl is increased. This is significant considering that results from in vitro studies (Category 1) indicate that under some conditions, oxycodone HCl may be preferentially extracted at higher levels compared to the extraction of naltrexone HCl as determined from percentage of label claim extracted. Naltrexone acts via competitive opioid receptor blockade to attenuate Drug Liking and High produced by oxycodone HCl administered IV. It is possible that with higher levels of oxycodone HCl compared to levels of naltrexone HCl, the competitive blockade would be partially overcome thereby allowing greater expression of Drug Liking and High following oxycodone HCl administration IV.

2. Results of in vitro studies (see below) demonstrate that intact Troxyca ER pellets may be manipulated for purposes of abuse. These manipulations result in the preferential extraction of oxycodone into an immediate release form without the presence of naltrexone. In vitro chemical extraction studies demonstrate that upon crushing, the controlled release properties of Troxyca ER pellets for oxycodone and naltrexone are substantially compromised resulting in immediate release of both substances into various solvents (b) (4)

(b) (4)

(b) (4)

### 3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. Consideration should be given to allowing language in Section 9.2 of the label indicating that upon crushing Troxyca ER capsules, oxycodone HCl and naltrexone HCl are released.
2. Consideration should be given to allowing language in Section 9.2 of the label describing human abuse potential studies B4531008 and B4531009. These studies do provide support for deterrent effects of crushed Troxyca ER to oral and intranasal abuse and should be allowed in the label.

(b) (4)

3. Consideration should also be given to allowing a description of simulated intravenous study B4981002 in section 9.2 of the label. This study did provide evidence that the presence of 12% naltrexone in the Troxyca ER formulation can block subjective effects of the available oxycodone assuming all naltrexone is released as is the case with crushing Troxyca ER contents.

## II. Discussion

### 1. Chemistry

#### 1.1 Substance information

Troxyca ER is formulated as pellets containing sequestered naltrexone HCl and extended release oxycodone HCl.

(b) (4)

According to Sponsor, naltrexone HCl remains sequestered if taken as directed but is released if crushed or chewed, antagonizing the pharmacodynamic (PD) effects of oxycodone, including Drug Liking and High. Troxyca ER is formulated as extended release pellets and contained in a hard gelatin capsule for oral administration at 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg oxycodone HCl/naltrexone HCl, respectively,

(b) (4)

Each Troxyca ER pellet consists of the following layers:

(b) (4)

## 4. Clinical Studies

### 4.1 Human abuse potential studies

Sponsor conducted two naltrexone dose ratio/abuse potential studies in order to determine the appropriate ratio of naltrexone HCl to oxycodone HCl to be used in the to-be-marketed formulations. These two studies, namely study ALO-02-07-201 and study ALO-02-09-2001, used commercially available oxycodone HCl and naltrexone HCl to create selected ratios of oxycodone to naltrexone (ranging from 4% to 24% naltrexone) to administer orally and evaluate subjective effects including Drug Liking VAS. Based on the results of these studies, Sponsor elected to use in the to-be-marketed formulation an oxycodone HCl to naltrexone HCl ratio (b) (4) representing 12% naltrexone. It should be stressed that these studies did not use the to-be-marketed formulation Troxyca ER Capsules and will not be further discussed in this review.

In support of possible abuse deterrent effects for Troxyca ER Capsules, as part of this NDA 207-621 Sponsor submitted the following three human abuse potential studies:

- Oral HAP Study B4531008 entitled “A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, 6-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release and Placebo When Administered Orally to Non-Dependent, Recreational Opioid Users.” Study was started February 12, 2013 and completed August 9, 2013. Final report was dated May 27, 2014.
- Intranasal HAP Study B4531009 entitled “A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, 4-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release, and Placebo When Administered Intranasally to Non-Dependent, Recreational Opioid Users.” Study was initiated July 17, 2013 and completed on July 17 2013. Final study reported was date April 15, 2014.

- Intravenous HAP Study B4981002 entitled “A Randomized, Single-Dose, Placebo-Controlled, Double-Blind, 3-Way Crossover Study to Determine the Relative Abuse Potential of Intravenous Oxycodone Hydrochloride Alone or in Combination with Intravenous Naltrexone Hydrochloride in Opioid Experienced Non-Dependent Subjects.” First subject entered study July 9, 2013 and last subject completed study September 24 2013. Final study report was dated May 5, 2014.

At the request of CSS, CDER Office of Biostatistics conducted statistical reviews for studies B4531008, B4531009, and B4981002. (DARRTS, NDA 207621, September 14, 2015, Author: Ling Chen, Ph.D.)

### ***Oral Study B4531008***

Study B4531008 is a randomized, double-blind, double-dummy, placebo, and active-controlled, 6-way crossover study in healthy, non-dependent, recreational opioid users. Study includes a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objectives include:

- To determine the relative abuse potential of intact and crushed ALO-02 60 mg/7.2 mg compared to crushed oxycodone HCl IR 60 mg and placebo administered orally to non-dependent, recreational opioid users.
- To determine the relative abuse potential of crushed ALO-02 40 mg/4.8 mg compared to crushed oxycodone HCl IR 40 mg and placebo when administered orally to non-dependent, recreational opioid users.

Secondary objectives include:

- To evaluate the PK profile of oxycodone, noroxycodone, oxymorphone, naltrexone, and 6- $\beta$ -naltrexol following oral administration of (crushed and intact) ALO-02, and crushed oxycodone HCl IR in non-dependent, recreational opioid users.
- To compare the safety of intact and crushed ALO-02 with crushed oxycodone HCl IR when administered orally in non-dependent, recreational opioid users.

### **Methodology**

A total of 32 recreational opioid users completed the Treatment Phase and constituted the Completer Population used for primary PD analysis. A total of 41 subjects initially randomized to the Treatment Phase constituted both the Safety and PK population. All subjects were non-dependent to opioids based on DSM-IV-TR criteria. A recreational opioid user was defined as a user of opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the previous year and at least once in the 8 weeks before the Screening Visit (Visit 1).

All subjects were required to fast for at least 8 hours before and 2 hours after each drug administration in the Drug Discrimination Phase (Visit 2) and Treatment Phase (Visits 3-8).

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments listed below, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- Oxycodone IR 40 mg (2 x 20 mg oxycodone IR tablets crushed in solution) administered orally
- Placebo solution administered orally.

Pharmacodynamic and safety assessments conducted during the Drug Discrimination Phase were conducted at pre-dose and up to 5 hours post-dose. In order to advance to the Treatment Phase, subjects were required to:

- Distinguish oxycodone from placebo on select subjective drug measures (ie,  $\geq 15$  points peak increase for Drug Liking and Take Drug Again, and  $\geq 30$  points peak increase for High within 2 hours following dosing with oxycodone relative to placebo) when administered IV. A peak score of  $\geq 65$  must have been indicated on bipolar measures of Drug Liking within 2 hours post-dose and Take Drug Again at 5 hours post-dose in response to oxycodone.
- Display an acceptable placebo response, defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again.
- Tolerate study treatments safely (i.e. no episodes of vomiting within the first 4 hours post-dose).
- Demonstrate general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

Treatment Phase consisted of 6 treatment periods each with a 2-night confined stay, where each dosing was separated by a washout period of a minimum of 5 days and did not exceed 14 days. Treatments were randomized according to a Williams Square design. During each Treatment Period, subjects received a single dose of the treatments listed in Table 3 in a randomized, double-blind, double-dummy crossover manner:

Table 6. Oral Treatments Administered In A Randomized, Double-Blind, Double-Dummy (Solution and Solid Dosing Forms) Crossover Manner (Source: Table 1 of Protocol Amendment 1 for Study B4531008)

| Treatment Arm                                  | Solution                                      | Solid Dosing Form                            |
|--|---|--|
| Treatment A<br>Placebo                         | Placebo Solution                              | Placebo (to match Troxyca ER) Intact         |
| Treatment B<br>Troxyca ER 60 mg/7.2 mg Intact  | Placebo Solution                              | Troxyca ER (1 x 60 mg/7.2 mg Capsule) Intact |
| Treatment C<br>Troxyca ER 60 mg/7.2 mg Crushed | Troxyca ER (1 x 60 mg/7.2mg Capsule) Crushed  | Placebo (to match Troxyca ER) Intact         |
| Treatment D<br>Oxycodone IR 60 mg Crushed      | Oxycodone HCl IR (3 x 30 mg Tablets) Crushed  | Placebo (to match Troxyca ER) Intact         |
| Treatment E<br>Troxyca ER 40 mg/4.8 mg Crushed | Troxyca ER (1 x 40 mg/4.8 mg Capsule) Crushed | Placebo (to match Troxyca ER) Intact         |
| Treatment F<br>Oxycodone IR 40 mg Crushed      | Oxycodone HCl IR (2 x 20 mg Tablets) Crushed  | Placebo (to match Troxyca ER) Intact         |

Troxyca ER capsule contents (1 x 40 mg/4.8 mg capsule and 1 x 60 mg/7.2 mg capsule) and oxycodone IR tablets (2 x 20 mg tablets and 3 x 20 mg tablets) were crushed (b) (4) Placebo solution was prepared (b) (4)

Subjects were instructed to swallow intact study medication whole, not to open the capsules, and not chew medication prior to swallowing. All study treatments that were crushed during the Treatment

Phase were administered as a solution (containing either active study drug or placebo) and were administered orally in a dark, opaque cup or bottle, to maintain the integrity of the blinding.

Blood samples for pharmacokinetic (PK) measures were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 14, 24, and 36 hours post-dose. Pharmacokinetic endpoints determined of oxycodone and naltrexone and examined in this review include

- $C_{max}$  = maximum plasma concentration achieved
- $T_{max}$  = time to reach  $C_{max}$
- $AUC_{0-2hrs}$  = area under the plasma concentration-time curve from time 0 to 2 hour post-dose
- $AUC_{inf}$  = area under the plasma concentration-time curve from time 0 extrapolated to infinity.

For the purposes of this review focus will be placed on the following pharmacodynamic measures:

- Primary measure of bipolar 100 point Drug Liking VAS –  $E_{max}$  and  $AUE_{0-2hrs}$ , as well as  $TE_{max}$
- Primary measure of unipolar 100 point High VAS –  $E_{max}$  and  $AUE_{0-2hrs}$ , as well as  $TE_{max}$

$E_{max}$  is defined as the maximum drug effect.  $TE_{max}$  is the time required to achieve  $E_{max}$ .  $AUE_{0-2hrs}$  represents area under the effect curve from 0 to 2 hours post-dose, reflecting cumulative drug effect (drug liking or high) over that time period.

All pharmacodynamic analyses were performed using the Completer Population which included all randomized subjects who complete all 6 periods of the Treatment Phase and who contributed post-dose PD data from each period. This population was analyzed as randomized.

## Study Results

### Disposition of Subjects

Of the 81 subjects screened, 75 eligible subjects participated in the Naloxone Challenge Phase, of which 72 subjects completed and 3 subjects were discontinued; 2 subjects due to adverse events not related to study drug and 1 subject discontinued because the entrance criteria was not met.

Seventy-two (72) subjects entered the Drug Discrimination Phase, of which, 31 subjects discontinued and 41 subjects successfully completed the Drug Discrimination Phase. Five (5) subjects were discontinued after treatment with crushed oxycodone HCl IR 40 mg and 1 subject was discontinued after treatment with placebo due to AEs (not related to study drug). Nine (9) subjects treated with crushed oxycodone HCl IR 40 mg and 10 subjects treated with placebo were discontinued as they did not meet entrance criterion (not related to study drug). Three (3) subjects in the crushed oxycodone HCl IR 40 mg and 3 subjects treated with placebo were discontinued due to protocol violations.

In the Treatment Phase, 41 subjects were randomized to the Treatment Phase and constituted both the Safety and PK population. A total of 32 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis; 9 subjects discontinued during the Treatment Phase. The primary reasons for discontinuation were: 5 subjects due to positive UDS results (protocol violation), 2 subjects due to AEs (related to study drug), 1 subject was lost to follow-up and 1 subject withdrew consent.

## Results - Pharmacokinetics

Table 7 provides the resulting pharmacokinetic parameters for oxycodone in plasma for active treatments. Oxycodone  $C_{max}$ ,  $AUC_{0-2hrs}$ , and  $AUC_{inf}$  were statistically similar when comparing oral crushed Troxyca ER 40 mg/4.8 mg to crushed oxycodone IR 40 mg. Likewise, these same three pK parameters for oxycodone were statistically similar when comparing crushed Troxyca ER 60 mg/7.2 mg to crushed oxycodone IR 60 mg. For all four crushed treatments, the median time to  $C_{max}$  ( $T_{max}$ ) was approximately 1 hour. These observations indicate that with crushing, the oxycodone extended release properties of the Troxyca ER formulation are severely compromised resulting in immediate release of the oxycodone. By contrast, as expected of an oxycodone extended release formulation, intact Troxyca ER 60 mg displayed a significantly lower oxycodone  $C_{max}$  and a much longer median  $T_{max}$ , compared to following crushed Troxyca ER 60 mg treatment (See Table 7).

Table 7. Summary of Plasma Oxycodone Pharmacokinetic Parameters Following Oral Administration of Crushed and Intact Troxyca ER Capsules and Crushed Oxycodone IR Tablets. (Source: Table 42 on page 170 of the Full Clinical Study Report for Protocol B4531008)

| Parameter   | Crushed Troxyca ER 40mg /4.8 mg | Crushed Oxycodone IR 40 mg | Intact Troxyca ER 60 mg/7.2 mg | Crushed Troxyca ER 60 mg/7.2 mg | Crushed Oxycodone IR 60 mg |
|---|---------------------------------|----------------------------|--------------------------------|---------------------------------|----------------------------|
| <b>Number of Subjects</b>                                       | 36                              | 37                         | 38                             | 37                              | 36                         |
| <b>C<sub>max</sub></b> (ng/mL)<br>(Geometric Mean & %CV)        | 76.31<br>(29)                   | 64.95<br>(24)              | 28.53<br>(31)                  | 111.5<br>(26)                   | 87.03<br>(31)              |
| <b>T<sub>max</sub></b> (hrs)<br>(Median and Range)              | 1.03<br>(0.53-2.55)             | 1.03<br>(0.28-3.07)        | 12.1<br>(3.03-14.1)            | 0.58<br>(0.53-1.55)             | 1.04<br>(0.30-2.55)        |
| <b>AUC<sub>0-2hrs</sub></b> (ng.h/mL)<br>(Geometric Mean & %CV) | 99.97<br>(27)                   | 85.82<br>(24)              | 0.65<br>(77)                   | 394.0<br>(24)                   | 49.94<br>(39)              |
| <b>AUC<sub>inf</sub></b> (ng h/mL)<br>(Geometric Mean & %CS)    | 348.1<br>(31)                   | 350.5<br>(28)              | 629.4<br>(28)                  | 503.5<br>(28)                   | 516.6<br>(33)              |

Naltrexone was observed in plasma following treatments with either dose of crushed Troxyca ER but not following treatment with intact Troxyca ER 60 mg/7.2 mg. The naltrexone  $C_{max}$  following treatments with crushed Troxyca ER 40 mg/4.8 mg and crushed Troxyca ER 60 mg/7.2 mg were 1.074 ng/mL and 1.810 ng/mL. For both crushed treatments, the median naltrexone  $T_{max}$  was approximately 0.5 hours.

## Results - Pharmacodynamic

Statistical analyses of  $E_{max}$  of Drug Liking VAS and of High VAS, including percentage reduction in  $E_{max}$  response, were conducted by the CDER Office of Biostatistics. Statistical analysis was based on a mixed-effects model which included sequence, treatment, and period as fixed effects, and subject as a random effect. Hypothesis testing was conducted with a margin of 0.

## Drug Liking VAS

Descriptive statistics for Drug Liking VAS are shown in Table 8 below.

Table 8. Descriptive Summary of Primary Measure of Drug Liking VAS in the Completer Population (N=32). (Data obtained from CDER Office of Biostatistics and from Table 11 on pages 75 of Full Clinical Study Report for Protocol B4531008.)

|  | Placebo      | Crushed Troxyca ER 40mg /4.8 mg | Crushed Oxycodone IR 40 mg | Intact Troxyca ER 60 mg/7.2 mg | Crushed Troxyca ER 60 mg/7.2 mg | Crushed Oxycodone IR 60 mg |
|--|--------------|---------------------------------|----------------------------|--------------------------------|---------------------------------|----------------------------|
| <b>E<sub>max</sub></b> (Points)        |              |                                 |                            |                                |                                 |                            |
| Mean (SE)                              | 51.6 (0.66)  | 70.1 (3.40)                     | 85.5 (2.85)                | 59.3 (2.67)                    | 74.4 (3.20)                     | 89.7 (2.40)                |
| Median                                 | 50.5         | 64.5                            | 90.5                       | 51                             | 73                              | 99.5                       |
| (Q1,Q3)                                | (50, 51)     | (51.5, 91.25)                   | (74.25, 100)               | (51, 60)                       | (58, 94)                        | (78.25, 100)               |
| Range (min,max)                        | 50-68        | 50-100                          | 50-100                     | 50-100                         | 50-100                          | 57-100                     |
| LS Mean (SE)                           | 51.5 (0.67)  | 70.1 (3.46)                     | 85.4 (2.81)                | 59.2 (2.67)                    | 74.4 3.14)                      | 89.8 (2.34)                |
| LCL,UCL                                | 50.1, 52.9   | 63.0, 77.2                      | 79.6, 91.1                 | 53.8, 64.7                     | 68.0, 80.8                      | 85, 94.5                   |
| <b>TE<sub>max</sub></b> (h)            |              |                                 |                            |                                |                                 |                            |
| Mean (SD)                              | 0.84 (1.13)  | 2.54 (4.79)                     | 1.55 (2.49)                | 3.55 (4.75)                    | 2.15 (4.40)                     | 1.741 (4.13)               |
| Median                                 | 0.27         | 1.02                            | 1.02                       | 0.76                           | 1.02                            | 1.01                       |
| Range (min,max)                        | (0.25, 5.02) | (0.25, 24.02)                   | (0.27, 14.02)              | (0.25, 14.02)                  | (0.25, 24.02)                   | (0.25, 24.02)              |
| <b>AUE<sub>0-2h</sub></b> (h x points) |              |                                 |                            |                                |                                 |                            |
| Mean (SD)                              | 100 (5.15)   | 118.5 (28.77)                   | 141.3 (32.92)              | 100.2 (10.64)                  | 127.3 (31.29)                   | 149.5 (24.19)              |
| Median                                 | 100          | 108.56                          | 146.06                     | 100.13                         | 121.94                          | 154.88                     |
| (Q1,Q3)                                | (100, 100.5) | (100.1, 140.5)                  | (119.8, 169.1)             | (100, 101.0)                   | (105.3, 145.4)                  | (129.4, 170.0)             |
| Range (min, max)                       | 75.0-111.5   | 46.3-181.3                      | 53.8-181.5                 | 66.9-137.0                     | 62.3-193.8                      | 104.6-181.3                |
| LS Mean                                | 100.1        | 118.4                           | 141.3                      | 100.1                          | 127.3                           | 149.5                      |
| 95% CI                                 | 91.4, 108.9  | 109.6, 127.1                    | 132.5, 150.1               | 91.4, 108.9                    | 118.5, 136.0                    | 140.7, 158.3               |

Statistical analysis for E<sub>max</sub> of drug liking revealed the following:

- Oral crushed Oxycodone IR at doses of 40 mg and 60 mg produced E<sub>max</sub> of Drug Liking (LS means of 85.5 mm and 89.7 mm, respectively) that were significantly (p<0.0001) higher than the E<sub>max</sub> of Drug Liking produced by placebo (LS mean of 51.6 mm), thereby validating the study with respect to Drug Liking VAS.
- The E<sub>max</sub> of Drug Liking following Oral crushed Troxyca ER 40 mg/4.8 mg (LS mean 70.2 mm) was significantly lower (p=0.0011) than that produced by oral crushed Oxycodone IR 40 mg (LS mean of 85.5 mm) but significantly (p<0.0001) higher than the E<sub>max</sub> of Drug Liking produced placebo (LS mean 51.6 mm).
- The E<sub>max</sub> of Drug Liking following Oral crushed Troxyca ER 60 mg/7.2 mg (LS mean 74.5 mm) was significantly lower (p=0.0002) than that produced by oral crushed Oxycodone IR 60 mg (LS mean of 89.8 mm) but significantly (p<0.0001) higher than the E<sub>max</sub> of Drug Liking produced placebo (LS mean 51.6 mm) or by intact oral Troxyca ER 60 mg/7.2 mg (LS mean of 74.5 mm) (p=0.0004).

The median  $TE_{max}$  values were similar (approximately 1 hour) across all for active crushed treatments. This corresponds to the  $T_{max}$  for oxycodone in plasma achieved with a median of about 1 hour for all four crushed treatments (see Table 7)

Cumulative drug liking experience ( $AUE_{0-2hrs}$ ) over the first 2 hours following oral crushed Troxyca ER 40 mg/4.8 mg (LS mean of 118.4 h\*mm ) or crushed Troxyca ER 60 mg (LS mean of 127.3 h\*mm ) were significantly ( $p<0.0001$ ) below that following oxycodone IR 40 mg or 60 mg (141.3 and 149.5 h\*mm), respectively. On the other hand, oral crushed Troxyca ER at doses of 40 mg/4.8mg and 60 mg/7.2 mg had  $AUC_{0-2hrs}$  that were significantly above that produced by placebo (LS mean of 100.1 h\*mm).

#### Percentage Reduction Analysis for $E_{max}$ of Drug Liking

Among 32 completers, approximate 28% (9) subjects had no reduction in  $E_{max}$  of Drug Liking, and 63% (20) and 53% (17) of subjects had at least 30% and 50% reduction in  $E_{max}$  of Drug Liking for crushed Troxyca ER 40mg/4.8 mg compared to crushed IR oxycodone 40 mg. Out of 32 subjects, 25% (8) of subjects had no reduction in  $E_{max}$  of Drug Liking, and 59% (19) and 44% (14) of subjects has a least 30% and 50% reduction in  $E_{max}$  of Drug Liking for Troxyca ER 60mg/7.2 mg compared to crushed IR oxycodone 60 mg.

#### High VAS

Descriptive statistics for  $E_{max}$ ,  $TE_{max}$ , and  $AUE_{0-2hrs}$  using High VAS are provided in Table 9 below.

Statistical analysis for  $E_{max}$  of drug liking revealed the following:

- Oral crushed Oxycodone IR at doses of 40 mg and 60 mg produced  $E_{max}$  of High (LS means of 78.6 mm and 85.7 mm, respectively) that were significantly ( $p<0.0001$ ) greater than the  $E_{max}$  of High produced by placebo (LS mean of 10.2), thereby validating the study with respect to High VAS.
- The  $E_{max}$  of High following Oral crushed Troxyca ER 40 mg (LS mean 47.3 mm) was significantly lower ( $p=0.0099$ ) than that produced by oral crushed Oxycodone IR 40 mg (LS mean of 77.9 mm) but significantly greater ( $p<0.0001$ ) than the  $E_{max}$  of Drug Liking produced placebo (LS mean 10.9 mm).
- The  $E_{max}$  of High following oral crushed Troxyca ER 60 mg (LS mean 52.8 mm) was significantly lower ( $p=0.0048$ ) than that produced by oral crushed Oxycodone IR 60 mg (LS mean of 85.7 mm) but significantly ( $p<0.0001$ ) greater than the  $E_{max}$  of Drug Liking produced placebo (LS mean 10.2 mm) or by intact oral Troxyca ER 60 mg (LS mean of 22.5 mm) ( $p=0.0002$ ).

Median  $TE_{max}$  values for High were around 1 hour for the four active crushed treatments.

Cumulative experience of High ( $AUE_{0-2hrs}$ ) over the first 2 hours following oral Troxyca ER 40 mg/4.8 mg (LS mean of 55.4 h\*mm ) or Troxyca ER 60 mg (LS mean of 71.6 h\*mm ) were significantly ( $p<0.0001$ ) below that following oxycodone IR 40 mg or 60 mg (112.1 h\*mm and 117.7 h\*mm), respectively. On the other hand, oral Troxyca ER at doses of 40 mg/4.8mg and 60 mg/7.2 mg had  $AUC_{0-2hrs}$  that were significantly greater than that produced by placebo (LS mean of 2.8 h\*mm).

Table 9. Descriptive Summary of Primary Measure of Unipolar High VAS – Completer Population (N=32). (Data obtained from CDER Office of Biostatistics and from Table 14 on page 82 of the Full Clinical Study Report for Protocol B4531008.

|  | Placebo       | Crushed Troxyca ER 40mg /4.8 mg | Crushed Oxycodone IR 40 mg | Intact Troxyca ER 60 mg/7.2 mg | Crushed Troxyca ER 60 mg/7.2 mg | Crushed Oxycodone IR 60 mg |
|--|---------------|---------------------------------|----------------------------|--------------------------------|---------------------------------|----------------------------|
| <b>E<sub>max</sub></b> (Points)        |               |                                 |                            |                                |                                 |                            |
| Mean (SE)                              | 10.9 (3.64)   | 47.3 (6.52)                     | 77.9 (4.50)                | 21.7 (6.25)                    | 53.4 (6.13)                     | 84.7 (4.18)                |
| Median                                 | 0             | 58                              | 87                         | 4                              | 60                              | 95.5                       |
| (Q1,Q3)                                | (0,2)         | (4.5, 83)                       | (67, 99)                   | (0,36.75)                      | (16.25, 88.5)                   | (78, 100)                  |
| Range (min,max)                        | 0-54          | 0-100                           | 0-100                      | (-46)-100                      | 0-100                           | 21-100                     |
| LS Mean (SE)                           | 10.2 (4.94)   | 46.6 (6.28)                     | 78.6 (4.41)                | 22.3 (5.93)                    | 52.8 5.70)                      | 85.6 (4.37)                |
| 95% CI                                 | 0.1, 20.3     | 33.9, 59.2                      | 69.6, 87.5                 | 10.4, 34.3                     | 41.4, 64.3                      | 76.7, 94.5                 |
| <b>TE<sub>max</sub></b> (h)            |               |                                 |                            |                                |                                 |                            |
| Mean (SD)                              | 1.83 (4.80)   | 1.30 (1.27)                     | 1.21 (0.70)                | 4.70 (5.71)                    | 1.45 (1.38)                     | 1.28 (0.80)                |
| Median                                 | 0.25          | 1.02                            | 1.02                       | 0.77                           | 1.02                            | 1.02                       |
| Range (min,max)                        | (0.25, 24.02) | (0.25, 6.00)                    | (0.27, 4.00)               | (0.25, 14.03)                  | (0.25, 8.03)                    | (0.48, 3.03)               |
| <b>AUE<sub>0-2h</sub></b> (h x points) |               |                                 |                            |                                |                                 |                            |
| Mean (SD)                              | 2.50 (8.30)   | 55.25 (54.13)                   | 112.08 (43.70)             | 9.90 (21.19)                   | 71.25 (55.98)                   | 117.58 (42.22)             |
| Median                                 | 0             | 40.88                           | 121.23                     | 0                              | 64.56                           | 128.56                     |
| (Q1,Q3)                                | (0.00, 0.00)  | (3.81, 102.13)                  | (96.0, 135.25)             | (0.00, 8.75)                   | (19.25,118.56)                  | (91.88,151.63)             |
| Range (min, max)                       | 0.00-34.88    | 0.00-168.00                     | 0.00-167.63                | 0.00-97.75)                    | 0.00-187.50                     | 22.75-162.50               |
| LS Mean                                | 2.8           | 55.4                            | 112.1                      | 9.7                            | 71.6                            | 117.7                      |
| 95% CI                                 | -12.2, 17.8   | 40.4, 70.4                      | 97.1, 127.1                | -5.3, 24.7                     | 56.6, 86.6                      | 102.7, 132.7               |

### Percentage Reduction Analysis for E<sub>max</sub> of High VAS

Among 32 completers, approximate 22% (7) subjects had no reduction in E<sub>max</sub> of High, and 53% (17) and 38% (12) of subjects had at least 30% and 50% reduction in E<sub>max</sub> of High for crushed Troxyca ER 40mg/4.8 mg compared to crushed IR oxycodone 40 mg. Out of 32 subjects, 22% (7) of subjects had no reduction in E<sub>max</sub> of High, and 47% (15) and 44% (14) of subjects had a least 30% and 50% reduction in E<sub>max</sub> of High for Troxyca ER 60mg/7.2 mg compared to crushed IR oxycodone 60 mg.

### Conclusions Regarding Study

The results obtained using the primary endpoints of E<sub>max</sub> and AUE<sub>0-2hrs</sub> for Drug Liking VAS and High VAS indicate that oral administration of crushed Troxyca ER at doses of 40 mg/4.8mg and 60 mg/7.2 mg is associated with drug liking and high consistent with having an abuse potential. However, the degree of Drug Liking and High produced by crushed Troxyca ER at either dose is significantly lower than that produced by oral crushed oxycodone IR at doses of 40 mg and 60 mg, respectively. These results suggest that oral crushed Troxyca ER may be associated with a lower abuse potential than oral crushed oxycodone IR at similar doses. The lower scores for E<sub>max</sub> of Drug liking and High associated with crushed Troxyca ER compared to crushed oxycodone IR treatments, at similar doses, is not due to differences in bioavailability of oxycodone since corresponding treatments result is similar oxycodone

plasma  $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-3hrs}$ . This leaves open the possibility that the differences result from the antagonism by naltrexone of oxycodone induced Drug Liking and High.

### ***Intranasal HAP Study B4531009***

Study B4531009 Study was a single center, randomized, double-blind, placebo and active-controlled, 4-way crossover study in healthy, non-dependent, recreational opioid users. Study includes a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objective was to determine the relative abuse potential of crushed Troxyca ER compared to crushed oxycodone HCl IR and placebo administered intranasally (IN) in non-dependent, recreational opioid users.

Secondary objective includes:

- To estimate the bioavailability of oxycodone and determine the PK profile of oxycodone noroxycodone, oxymorphone, naltrexone, and 6- $\beta$ -naltrexol following IN administration of crushed ALO-02 and crushed oxycodone HCl IR in non-dependent, recreational opioid users.
- To compare the safety of Troxyca ER with oxycodone HCl IR when crushed and administered intranasally in non-dependent, recreational opioid users.

### **Methodology**

A recreational opioid user was defined as a user of opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks before the Screening Visit (Visit 1). Subjects were required to have had experience with intranasal (IN) opioid administration, defined as IN use on at least 3 occasions within the last year before Screening.

A total of 28 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis. Thirty-two subjects constituted the safety and pharmacokinetic (PK) populations.

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- IN Oxycodone HCl IR 30 mg (3 x 10 mg oxycodone IR tablets crushed)
- IN Placebo (crushed lactose tablet, weight matched to oxycodone IR tablet).

Pharmacodynamic and safety assessments conducted during the Drug Discrimination Phase were conducted at pre-dose and up to 5 hours post-dose. In order to advance to the Treatment Phase, subjects were required to:

- Distinguish oxycodone from placebo on select subjective drug measures (ie,  $\geq 15$  points peak increase for Drug Liking and Take Drug Again, and  $\geq 30$  points peak increase for High within 2 hours following dosing with oxycodone relative to placebo) when administered IV. A peak score of  $\geq 65$  must have been indicated on bipolar measures of Drug Liking within 2 hours post-dose and Take Drug Again at 5 hours post-dose in response to oxycodone.
- Display an acceptable placebo response (defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again).

- Tolerate study treatments safely (ie, SpO2 >90%, no episodes of vomiting within the first 2 hours post-dose).
- Demonstrate general behavior suggestive that the subject could complete the study, as judged by the study center staff.

During the Treatment Phase single doses were administered to subjects in a randomized, double-blind, 4-way crossover fashion on Day 1 of each Treatment Period. Treatments were randomized according to Williams Square design. Subjects were required to fast for at least 8 hours before and 2 hours after each drug administration in the Treatment Phase. Treatments are described in Table 10 below.

Table 10. Intranasal (IN) Treatments Administered During the Treatment Phase. (Source: Table 3 on page 44 of the Full Clinical Study Report for Protocol B4531009)

| Treatment Arm | Treatment   | Weight of Powder |
|---------------|---|------------------|
| A             | Placebo (sugar spheres) crushed, weight matched to Troxyca ER capsule fill weight | (b) (4)          |
| B             | Troxyca ER 30 mg/3.16 mg (1 x 30 mg/3.6 mg capsule crushed)                       | (b) (4)          |
| C             | Placebo (lactose tablets) crushed, weight matched to oxycodone IR (3 x 10 mg)     | (b) (4)          |
| D             | Oxycodone IR 30 mg (3 x 10 mg tablets crushed)                                    | (b) (4)          |

The weights and crushed (b) (4) volumes of the Troxyca ER 30 mg/3.6 mg capsule and the oxycodone IR 3 × 10 mg tablets differed (b) (4) mg versus (b) (4) mg, respectively). In order to reduce the risk of unblinding of the subjects during intranasal administration, this study utilized 2 placebo controls. Placebo lactose tablets were crushed and weight matched to the oxycodone IR 3 × 10 mg tablets, and placebo sugar spheres were crushed and matched to the Troxyca ER to fill weight.

Study treatment was to be administered in a double-blind fashion under the supervision of investigator site personnel and must have been completed within 5 minutes. All subjects were instructed to complete insufflation over a stainless steel dosing tray. The dosing tray was used to collect any drug product that was not fully insufflated by the subject, dropped from the insufflation straw onto the tray, or fell from the subject's nose immediately after insufflation. After administration, study staff inspected the vial, nose, and hands to ensure that the study drug had been insufflated adequately. If a sufficient residual amount of powder remained in the vial, study staff tapped the vial and instructed the subject to insufflate the remaining study drug. The visible drug product was collected from the dosing tray and returned to the dosing vial for recording of post-dose weight.

For the purposes of this review focus will be placed on the following pharmacodynamic measures:

- Primary measure of bipolar 100 point Drug Liking VAS –  $E_{max}$  and  $AUE_{0-2hrs}$
- Primary measure of unipolar 100 point High VAS –  $E_{max}$  and  $AUE_{0-2hrs}$
- Secondary measure of bipolar Take Drug Again VAS –  $E_{max}$
- Percentage of dose insufflated (mg %), which was based on a calculation of the weight of powder remaining (if any) following dosing.

Pharmacokinetic endpoints determined of oxycodone and naltrexone and examined in this review include

- $C_{max}$  = maximum plasma concentration achieved

- $T_{max}$  = time to reach  $C_{max}$
- $AUC_{2hr}$  = area under the plasma concentration-time curve from time 0 to 2 hour post-dose
- $AUC_{inf}$  = area under the plasma concentration-time curve from time 0 extrapolated to infinity.

The Subject-Rated Scale for Nasal Effects was used to assess burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion using a 6-point scale (0 = not present/no problem; 1 = very mild problem; 2 = mild/slight problem; 3 = moderate problem; 4 = severe problem; 5 = problem “as bad as can be”). The Subject-Rated Scale for Nasal Effects was presented individually and summarized descriptively by treatment for each time point and each endpoint ( $E_{max}$ ,  $TE_{max}$ ).

## Study Results

### Disposition of Subjects.

Forty five subjects (45) entered the Drug Discrimination Phase and a total of 32 subjects successfully completed the Drug Discrimination Phase. Three (3) subjects were discontinued after treatment with oxycodone HCl IR due to an AE and 1 subject was discontinued after treatment with placebo lactose due to a protocol violation. Nine (9) subjects completed drug discrimination procedures, but were discontinued because they did not meet the entrance criteria.

In the Treatment Phase, 32 subjects were randomized to the Treatment Phase and constituted both the Safety and PK populations (Section 9.4.1). A total of 28 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis. Four (4) discontinuations were observed during the Treatment Phase, all were due to positive drug screens, none of which were related to study drug.

### Percentage of Dose Insufflated

Subjects generally did not have problems in insufflating the various treatments. Only two subjects had less than 100% insufflations.

- One subject insufflated 95.4% dose for Troxyca ER 30 mg/3.6.
- One subject insufflated 79.9% of dose for oxycodone IR 30 mg. This subject displayed drug liking and high scores of 92 mm and 94 mm, respectively, following insufflation of 79.9% dose of oxycodone IR 30 mg.

### Pharmacokinetic Results

Pharmacokinetic parameters for oxycodone in plasma are provided in Table 11.

Intranasal administration of crushed Troxyca ER 30 mg/3.6 mg was associated with an approximately 30% reduction in oxycodone plasma  $C_{max}$  compared to intranasal treatment with crushed oxycodone IR 30 mg (geometric means of 56.37 ng/mL and 80.38 ng/mL, respectively).  $T_{max}$  was longer following crushed Troxyca ER 30 mg/3.6 mg (median  $T_{max}$  of 1.6 hours) compared with crushed oxycodone IR 30 mg (median  $T_{max}$  of 0.5 hours). Oxycodone systemic plasma exposure based on geometric mean  $AUC_{inf}$  was about 20% lower for crushed Troxyca ER 30 mg/3.6 mg compared with crushed oxycodone IR 30 mg.

Table 11. Summary of Plasma Oxycodone Pharmacokinetic Parameters Following Intranasal Administration of Crushed Troxyca ER Capsules 30 mg/3.6 mg and Crushed Oxycodone IR 30 mg Tablets. (Source: Table 43, page 135 of the Full Clinical Report for Protocol B4531009.)

| Parameter for Oxycodone in Plasma                               | Intranasal Crushed Troxyca ER 30 mg /3.6 mg | Intranasal Crushed Oxycodone IR 30 mg |
|---|---|---------------------------------------|
| <b>Number of Subjects</b>                                       | 30  | 32                                    |
| <b>C<sub>max</sub></b> (ng/mL)<br>(Geometric Mean & %CV)        | 56.37<br>(24)                               | 80.38<br>(24)                         |
| <b>T<sub>max</sub></b> (hrs)<br>(Median and Range)              | 1.59<br>(0.28-4.07)                         | 0.475<br>(0.28-1.07)                  |
| <b>AUC<sub>0-2hrs</sub></b> (ng.h/mL)<br>(Geometric Mean & %CV) | 78.27<br>(27)                               | 113.3<br>(24)                         |
| <b>AUC<sub>inf</sub></b> (ng h/mL)<br>(Geometric Mean & %CS)    | 346.8<br>(30)                               | 432.7<br>(28)                         |

Following intranasal administration of crushed Troxyca ER 30 mg/3.6 mg capsule contents, individual naltrexone C<sub>max</sub> were achieved within 0.3 to 1.6 hours post-dose with a median T<sub>max</sub> of 0.3 hours. C<sub>max</sub> was 4.372 ng/mL, and naltrexone total plasma exposure based on the geometric mean for AUC<sub>inf</sub> value was 10.71 ng\*h/mL.

### Pharmacodynamic Results

Statistical analyses of E<sub>max</sub> of Drug Liking VAS and of High VAS, including percentage reduction in E<sub>max</sub> response, were conducted by the CDER Office of Biostatistics. Hypothesis testing was conducted with a margin of 0.

### Drug Liking VAS

Descriptive statistics for Drug Liking VAS are shown in Table 12 below. Following Troxyca ER IN approximately 75% of subjects had a maximum drug liking (E<sub>max</sub>) at most 69.5 mm with a median of 57 mm. By contrast, following oxycodone IR IN approximately 75% of subjects had a maximum drug liking at least 91.3 mm with a median of 98.5 mm.

Statistical analysis conducted by CDER Office of Biostatistics revealed the following:

- Oxycodone IR 30 mg IN produced an E<sub>max</sub> of Drug Liking (92.8 mm) that was significantly (p=0.0000) above the E<sub>max</sub> of drug liking (51.3 mm) produced by placebo IN, thereby validating the study with respect to the Drug Liking VAS.
- Crushed Troxyca ER 30 mg IN resulted in a E<sub>max</sub> of Drug Liking (60.5 mm) that was significantly (p=0.0217) less than the E<sub>max</sub> of Drug Liking produced by oxycodone IR 30 mg IN (92.8 mm).
- Troxyca ER 30 mg IN resulted in a E<sub>max</sub> of Drug Liking (60.5 mm) that was not significantly different (p=0.2523) from the E<sub>max</sub> of Drug Liking produced by placebo (50.9 mm).

Table 12. Descriptive Statistics for Bipolar Drug Liking VAS Following Intranasal (IN) Treatments – Completer Population (N=28) (Data obtained from Table 12 (page 72) and Table 13 (page 73) of the Full Study Report for B4531009)

| Bipolar<br>“Drug Liking”<br>VAS        | Treatment A<br>Intranasal<br>Placebo<br>Sugar Spheres | Treatment B<br>Intranasal<br>Troxyca ER<br>30mg/3.6 mg | Treatment C<br>Intranasal<br>Placebo<br>Lactose Tablet | Treatment D<br>Intranasal<br>Oxycodone IR<br>30 mg |
|--|---|--|--|--|
| <b>E<sub>max</sub> (Points)</b>        |   |  |  |  |
| Mean (SE)                              | 50.9 (0.22)   | 60.5 (2.28)  | 51.3 (0.63)  | 92.8 (2.26)  |
| Median                                 | 51.0  | 57.0   | 51.0   | 98.5   |
| Q1,Q3)                                 | (50, 51)  | (51, 69.5)   | (50, 51)   | (91.25, 100)                                       |
| Range (min,max)                        | (50, 56)  | (50, 100)  | (50, 68)   | (50, 100)  |
| <b>TE<sub>max</sub> (h)</b>            |   |  |  |  |
| Mean (SD)                              | 0.78 (0.81)   | 1.49 (1.82)  | 1.15 (1.37)  | 0.95 (2.22)  |
| Median                                 | 0.38  | 0.76   | 0.5  | 0.38   |
| Range                                  | (0.25, 3.02)  | (0.25, 8.00)   | (0.23, 6.02)   | (0.25, 12.02)                                      |
| <b>AUE<sub>0-2h</sub> (h x points)</b> |   |  |  |  |
| Mean (SD)                              | 98.52 (6.76)  | 105.29 (21.37)   | 100.24 (3.32)  | 159.58 (32.16)                                     |
| Median                                 | 100.00  | 100.94   | 100.00   | 167.06   |
| Q1,Q3)                                 | (100.00, 100.63)                                      | (98.63, 114.25)  | (100.00, 100.69)                                       | (148.06, 182.50)                                   |
| Range (min, max)                       | (68.75, 106.00)                                       | (54.63, 167.75)  | (87.50, 111.63)  | (61.00, 193.75)                                    |
| LS Mean                                | 98.8  | 105.4  | 100.4  | 160.0  |
| 95 CI                                  | 91.3, 106.2   | 97.9, 112.8  | 92.9, 107.8  | 152.5, 167.4                                       |

The median TE<sub>max</sub> of Drug Liking was less than an hour following intranasal treatment with either Troxyca ER 30 mg or oxycodone IR 30 mg.

Cumulative Drug Liking experience (AUE<sub>0-2hrs</sub>) over the first 2 hours following intranasal administration of Troxyca ER 30 mg was significantly less than that following oxycodone IR 30 mg IN but similar to that following placebo IN.

#### Percentage Reduction Analysis for E<sub>max</sub> of Drug Liking

Among 28 completers, approximately 7% (2) of subjects did not have any reduction in E<sub>max</sub> of Drug Liking following Troxyca ER 30 mg IN compared to following oxycodone IR 30 mg IN. Approximately 89% (23) and 82% (23) of subjects had at least 30% and 50% reductions in E<sub>max</sub> of Drug Liking following Troxyca ER 30 mg relative to following oxycodone IR 30 mg IN

## High VAS

Descriptive statistics for High VAS are shown in Table 13 below. Following Troxyca ER IN approximately 75% of subjects had an  $E_{\max}$  of High at most 39 mm with a median of 19 mm. By contrast, following oxycodone IR IN approximately 75% of subjects had an  $E_{\max}$  Drug Liking at least 88 mm with a median of 93.5 mm.

Table 13. Descriptive Statistics for Primary Unipolar High VAS in the Completer Population (N=28). (Data was obtained from Table 15 (page 77) and Table 16 (page 78) of the Full Study Report for B4531009)

| Unipolar<br>“High”<br>VAS                   | Treatment A<br>Placebo<br>Sugar Spheres | Treatment B<br>Troxyca ER<br>30mg/3.6 mg | Treatment C<br>Placebo<br>Lactose Tablet | Treatment D<br>Oxycodone IR<br>30 mg |
|---|---|--|--|--------------------------------------|
| <b><math>E_{\max}</math> (Points)</b>       |   |  |  |                                      |
| Mean (SE)                                   | 2.2 (1.89)                              | 26.6 (5.37)                              | 6.0 (4.13)                               | 85.8 (4.60)                          |
| Median                                      | 0.0                                     | 19.0                                     | 0.0                                      | 93.5                                 |
| Q1,Q3)                                      | (0, 0)                                  | (0.25, 40)                               | (0, 0)                                   | (88, 100)                            |
| Range (min,max)                             | (0, 53)                                 | (0, 100)                                 | (-50, 60)                                | (0, 100)                             |
|   |   |  |  |                                      |
| <b><math>TE_{\max}</math> (h)</b>           |   |  |  |                                      |
| Mean (SD)                                   | 0.27 (0.05)                             | 1.87 (4.87)                              | 0.52 (0.68)                              | 0.65 (0.53)                          |
| Median                                      | 0.26                                    | 0.28                                     | 0.25                                     | 0.52                                 |
| Range (min,max)                             | (0.25, 0.52)                            | (0.25, 24.00)                            | (0.23, 3.00)                             | (0.25, 2.03)                         |
|   |   |  |  |                                      |
| <b><math>AUE_{0-2h}</math> (h x points)</b> |   |  |  |                                      |
| Mean (SD)                                   | 0.89 (3.51)                             | 27.75 (39.72)                            | 4.77 (20.05)                             | 135.67 (43.05)                       |
| Median                                      | 0.00                                    | 15.00                                    | 0.00                                     | 141.25                               |
| Q1,Q3)                                      | (0.00, 0.00)                            | (0.00, 33.44)                            | (0.00, 0.00)                             | (127.56, 165.38)                     |
| Range (min, max)                            | (0.00, 18.00)                           | (0.00, 158.00)                           | (0.00, 105.25)                           | (11.50, 187.50)                      |
| LS Mean                                     | 0.2                                     | 27.1                                     | 5.6                                      | 136.4                                |
| 95 CI                                       | -11.6, 12.0                             | 15.3, 38.9                               | -6.2, 17.5                               | 124.6, 148.2                         |
|   |   |  |  |                                      |

Statistical analysis revealed the following:

- Oxycodone IR 30 mg IN produced an  $E_{\max}$  of high (85.8 mm) that was significantly above the  $E_{\max}$  of High (7.0 mm) produced by placebo IN, thereby validating the study with respect to the High VAS.
- Troxyca ER 30 mg IN resulted in an  $E_{\max}$  of High (26.6 mm) that was significantly ( $p=0.0125$ ) below the  $E_{\max}$  of High produced by oxycodone IR 30 mg IN (85.8 mm).
- Troxyca ER 30 mg IN resulted in  $E_{\max}$  of High (26.6 mm) that was not significantly different ( $p=0.4297$ ) from the  $E_{\max}$  of High produced by placebo (2.2 mm).

The median  $TE_{\max}$  of High was approximately 3-fold longer following intranasal treatment with Troxyca ER 30 mg compared to following intranasal oxycodone IR 30 mg.

Cumulative experience of High ( $AUE_{0-2hrs}$ ) over the first 2 hours following intranasal administration of Troxyca ER 30 mg (27.75 h\*mm) was significantly less than that following oxycodone IR 30 mg IN (135.67 h\*mm).

#### Percentage Reduction Analysis for $E_{max}$ of High VAS

Among 28 completers, approximately 11% (3) of subjects did not have any reduction in  $E_{max}$  of High following Troxyca ER 30 mg IN compared to following oxycodone IR 30 mg IN. Approximately 79% (22) and 61% (17) of subjects had at least 30% and 50% reductions in  $E_{max}$  of High following Troxyca ER 30 mg relative to following oxycodone IR 30 mg IN, respectively.

#### Subject-Rated Scale for Nasal Effects

The mean and median scores for all the domains of the Subject-Rated Scale for Nasal Effects were low. For Burning, Need to Blow Nose, Facial Pain/Pressure the oxycodone IR group had slightly higher mean  $E_{max}$  than the Troxyca ER 30 mg/3.6 mg and the placebo treatments. Overall, there was trend towards oxycodone IR resulting in more nasal effects relative to the other treatments; however this effect was minor and not indicative of any clinically significant or severe nasal adverse reactions.

#### Conclusions

Crushed Troxyca ER 30 mg IN produced  $E_{max}$  values for Drug Liking and High that were significantly below that produced by oxycodone IR 30 mg IN but statistically similar to that of placebo. In addition, the  $AUE_{0-2hrs}$  for crushed Troxyca ER 30 mg IN for Drug Liking and High were significantly less than that following crushed oxycodone IR 30 mg, and in the case of Drug Liking, statistically similar to the  $AUE_{0-2hrs}$  produced by placebo. These data indicate little Drug Liking or High associated with crushed Troxyca ER 30 mg given intranasally. The data support a possible deterrent effect of Troxyca ER Capsules to intranasal abuse.

#### ***Intravenous Study B4981002 (Simulated IV administration of formulation)***

Study B4981002 a single-center, randomized, double-blind, placebo-controlled, 3-way crossover study in non-dependent, recreational, and otherwise healthy opioid users. Study includes a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objective was to determine the relative abuse potential of IV oxycodone HCl when combined with IV naltrexone HCl (ie, simulated IV administration of ALO-02) compared with an equivalent IV dose of oxycodone HCl alone and with IV placebo, when administered to non-dependent, recreational opioid users.

Secondary objectives included:

- To evaluate the PK of oxycodone, oxymorphone, noroxycodone, naltrexone, and 6- $\beta$ -naltrexol following administration of IV oxycodone HCl combined with IV naltrexone HCl and IV oxycodone alone, when administered IV to non-dependent, recreational opioid users.
- To evaluate the overall systemic exposure of oxycodone in the presence and absence of naltrexone.

- To assess the safety and tolerability of single doses of IV oxycodone and IV oxycodone combined with IV naltrexone in non-dependent, recreational opioid users.

## Methodology

A sufficient number of subjects were to be screened and qualified to enroll 30 subjects into the Treatment Phase to ensure that at least 27 subjects completed all 3 Periods of the Treatment Phase. Subjects who did not complete the study may have been replaced at the discretion of the Investigator and Sponsor. Subjects consisted of recreational opioid users defined as a user of opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 8 weeks before the Screening Visit (Visit 1). Non-therapeutic opioid use must include at least one of the following routes of administration: intranasal use on at least 3 occasions in the past year or IV use on at least one occasion within the past year prior to Screening.

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- Oxycodone HCl 20 mg IV push over 4 minutes ( $\pm 15$  seconds)
- Placebo (administered as 0.9% sodium chloride) IV push over 4 minutes ( $\pm 15$  seconds).

Pharmacodynamic and safety assessments conducted during the Drug Discrimination Phase were conducted at pre-dose and up to 5 hours post-dose. In order to advance to the Treatment Phase, subjects were required to:

- Distinguish oxycodone from placebo on select subjective drug measures (ie,  $\geq 15$  points peak increase for Drug Liking and Take Drug Again, and  $\geq 30$  points peak increase for High within 2 hours following dosing with oxycodone relative to placebo) when administered IV. A peak score of  $\geq 65$  must have been indicated on bipolar measures of Drug Liking within 2 hours post-dose and Take Drug Again at 5 hours post-dose in response to oxycodone.
- Display an acceptable placebo response (defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again).
- Tolerate study treatments safely (i.e., SpO<sub>2</sub> >90%, no episodes of vomiting within the first 2 hours post-dose).
- Demonstrate general behavior suggestive that the subject could complete the study, as judged by the study center staff.

The Treatment Phase consisted of 3 Treatment Periods, where each dosing was separated by a washout period of a minimum of 5 days, to target 7 days between dosing, not exceeding 21 days. During each Treatment Period, subjects (N=30) received a single dose of the treatment, randomized using a Williams Square design. Subjects were required to fast for at least 8 hours before and 2 hours after each drug administration in the Treatment Phase. Specific treatments administered are provided in Table 14.

Study was conducted as a parenteral simulation of an Troxyca ER formulation simulation study using solution preparations of oxycodone 20 mg and naltrexone 2.4 mg that are suitable for IV administration. The doses selected represent the exact amount of each product contained in an Troxyca ER 20 mg/2.4 mg capsule and is the maximum amount of oxycodone/naltrexone that would be liberated if an Troxyca ER mg/2.4 mg capsule were crushed and the contents solubilized in aqueous solution. Such tampering efforts are required by drug users who attempt to prepare such formulations for injection. In this study,

naltrexone and oxycodone were given simultaneously to mimic as closely as possible the injection of a solution derived from tampering with Troxyca ER.

Table 14. Study Treatments Administered. (Source: Table 3, page 45 of the Full Clinical Study Report for Protocol B4981002)

| Treatment | Designation  | Formulation   |
|-----------|--|---|
| A         | Placebo  | 0.9% sodium chloride IV push over 4 minutes $\pm$ 15 seconds  |
| B         | Simulated parenteral dose of Troxyca ER 20 mg/2.4 mg | Oxycodone HCl 20 mg IV + naltrexone HCl 2.4 mg simultaneously IV push over 4 minutes $\pm$ 15 seconds |
| C         | Oxycodone HCl 20 mg                                  | Oxycodone HCl 20 mg IV push over 4 minutes $\pm$ 15 seconds   |

This review will focus on the primary measures of Drug Liking VAS and High VAS. Drug Liking VAS is a 0 – 100 point bipolar VAS scale. High VAS is a unipolar 0 – 100 points scale. Primary endpoints were peak effect ( $E_{max}$ ) and area under the effect curve from 0 to 2 hours post-dose ( $AUE_{0-2hrs}$ ) as determined using the Drug Liking VAS and the High VAS. Other endpoints determined by Sponsor included  $AUE_{0-1hr}$ ,  $AUE_{0-8hrs}$ , and time to achieve peak effect ( $TE_{max}$ ).

Pharmacokinetic endpoints determined of oxycodone and naltrexone and examined in this review include

- $C_{5min}$  = concentration observed at 5 minutes after the start of infusion
- $AUC_{0-1hr}$  = area under the plasma concentration-time curve from time 0 to 1 hour post-dose
- $AUC_{0-2hrs}$  = area under the plasma concentration-time curve from time 0 to 2 hour post-dose
- $AUC_{0-8hrs}$  = area under the plasma concentration-time cure from time 0 to 8 hours post-dose
- $AUC_{inf}$  = area under the plasma concentration-time curve from time 0 extrapolated to infinity.

## Study Results

### Subject Disposition

Of 60 subjects screened, all passed the Naloxone Challenge Test and entered the Drug Discrimination Phase. Twenty-seven subjects did not complete the Drug Discrimination Phase. Five subjects were discontinued after treatment with oxycodone HCl 20 mg IV due to treatment-related adverse events. Seventeen (17) subjects completed drug discrimination procedures, but were discontinued because they did not meet randomization criteria for the Treatment Phase. One subject was discontinued after treatment with placebo due to unwillingness to participate in the study. Four (4) subjects were discontinued due to other reasons un-related to the study drug: 1 subject was withdrawn at the discretion of the site as he presented a likelihood that he would not complete the study; 1 subject withdrew from the study due to family emergency; 2 subjects discontinued as the number of randomized subjects required for this study had been fulfilled.

In the Treatment Phase, 33 subjects were randomized to the Treatment Phase and constituted both the Safety and PK populations. Three subjects were discontinued in the Treatment Phase due to testing positive in urine drug screens. A total of 29 subjects completed the Treatment Phase and constituted the Completer Population used for primary PD analysis.

## Pharmacokinetic Results

A summary of the plasma oxycodone pharmacokinetic parameters following intravenous injection of active treatments is provided in Table 15. The data show a similar pharmacokinetic profile for plasma oxycodone following intravenous injection of simulated Troxyca 20mg/2.4 mg and intravenous injection of oxycodone HCl 20 mg. Both treatments resulted in plasma oxycodone concentration at 5 minutes post-dosing of around 134-140 ng/mL. The partial AUCs for the different time periods were similar for the two treatments demonstrating similar systemic plasma oxycodone exposure.

Table 15. Summary of Plasma Oxycodone Pharmacokinetic Parameters Following Intravenous Administration of Simulated Troxyca 20 mg/2.4 mg and Oxycodone HCl 20 mg. (Source: Table 45 on page 131 of the Full Clinical Study Report for Protocol B4981002)

| Parameter for Oxycodone in Plasma                               | Intravenous Simulated Troxyca (Oxycodone HCL 20 mg/ naltrexone HCl 2.4 mg) | Intravenous Oxycodone HCl 20 mg |
|---|--|---------------------------------|
| <b>Number of Subjects</b>                                       | 32   | 30                              |
| <b>C<sub>5 min</sub></b> (ng/mL)<br>(Geometric Mean & %CV)      | 140.6<br>(56)  | 134.6<br>(40)                   |
| <b>T<sub>max</sub></b> (hrs)<br>(Median and Range)              | 0.150<br>(0.083-0.900)   | 0.150<br>(0.150-0.367)          |
| <b>AUC<sub>0-1hrs</sub></b> (ng.h/mL)<br>(Geometric Mean & %CV) | 85.19<br>(24)  | 89.25<br>(33)                   |
| <b>AUC<sub>0-2hrs</sub></b> (ng.h/mL)<br>(Geometric Mean & %CV) | 144.6<br>(20)  | 153.2<br>(33)                   |
| <b>AUC<sub>0-8hrs</sub></b> (ng.h/mL)<br>(Geometric Mean & %CV) | 319.5<br>(17)  | 339.0<br>(31)                   |
| <b>AUC<sub>inf</sub></b> (ng h/mL)<br>(Geometric Mean & %CS)    | 393.7<br>(16)  | 420.3<br>(30)                   |

Intravenous administration of simulated Troxyca 20mg/2.4 mg resulted in a geometric mean (%CV) C<sub>5min</sub> for plasma naltrexone of 12780 (44) pg/mL. The geometric mean (%CV) AUC<sub>1hr</sub>, AUC<sub>0-2hrs</sub> and AUC<sub>inf</sub>, reflecting systemic plasma exposure to naltrexone, were 6713 (31) pg\*hr/mL, 10450 pg\*hr/mL, and 17130 (31) pg\*hr/mL, respectively.

## Pharmacodynamic Results

Statistical analyses of E<sub>max</sub> of Drug Liking VAS and of High VAS, including percentage reduction in E<sub>max</sub> response, were conducted by the CDER Office of Biostatistics. Hypothesis testing was conducted with a margin of 0.

### Drug Liking VAS

Descriptive statistics for E<sub>max</sub> of Drug Liking are found in Table 16.

Validity of the study is indicated by the significantly ( $p=0.0000$ ) higher  $E_{max}$  of Drug Liking observed following oxycodone HCl 20 mg IV compared to placebo IV.

The  $E_{max}$  of Drug Liking produced by simulated Troxyca ER 20 mg IV (58.2 mm) was statistically smaller ( $p<0.0154$ ) than that produced by Oxycodone HCl 20 mg IV (92.4), but similar ( $p=0.0606$ ) to that produced by placebo IV (52.3 mm). Likewise simulated IV Troxyca ER resulted in a mean oxycodone  $AUC_{0-2hrs}$  (100.94) that was significantly lower than that produced by Oxycodone HCl 20 mg IV (152.43), but similar to that produced by IV placebo (100.94).

Table 16. Descriptive Summary of Primary Endpoint of Bipolar Drug Liking VAS (N=29 Subjects) (Source: CDER Office of Biostatistics and from Table 13 on page 76 of the Full Clinical Study Report for Protocol B4981002)

|                                    | Placebo         | Simulated Troxyca ER<br>20 mg/2.4 mg IV | Oxycodone HCl 20 mg<br>IV |
|------------------------------------|-----------------|---|---------------------------|
| <b>Emax (mm)</b>                   |                 |   |                           |
| Mean (SE)                          | 52.3 (0.99)     | 58.2 (3.32)                             | 92.4 (1.66)               |
| Median                             | 51.0            | 51.0                                    | 97.0                      |
| Q1,Q3)                             | (50, 51)        | (51, 62)                                | (86, 100)                 |
| Range (min,max)                    | (50, 75)        | (50, 100)                               | (69, 100)                 |
|                                    |                 |   |                           |
| <b>AUE<sub>0-2h</sub> (h x mm)</b> |                 |   |                           |
| Mean (SD)                          | 100.94 (3.76)   | 104.29 (8.37)                           | 152.43 (31.27)            |
| Median                             | 100.0           | 100.50                                  | 158.13                    |
| Q1,Q3)                             | (99,75, 100.21) | (100.0, 103.88)                         | (143.13, 170.42)          |
| Range (min, max)                   | (95.58, 112.83) | 97.46, 130.88)                          | (79.54, 197.92)           |
|                                    |                 |   |                           |

#### Percentage Reduction Analysis of $E_{max}$ of Drug Liking

Among 29 completers, approximately 10% (3) of subjects did not have any reduction in  $E_{max}$  of Drug Liking following simulated Troxyca ER 20 mg IV treatment compared to Oxycodone HCl 20 mg IV treatment. Approximately 90% (26) and 83% (24) of subjects had at least 30% and 50% reduction  $E_{max}$  of Drug Liking following Troxyca ER 20 mg IV treatment compared to Oxycodone HCl 20 mg IV treatment.

#### High VAS

Descriptive statistics for  $E_{max}$  of High are found in Table 17.

Validity of the study is indicated by the significantly ( $p=0.0000$ ) higher  $E_{max}$  of High observed following oxycodone HCl 20 mg IV compared to placebo IV.

The  $E_{max}$  of High VAS produced by simulated Troxyca ER 20 mg IV (17.4 mm) was statistically smaller ( $p<0.0197$ ) than that produced by Oxycodone HCl 20 mg IV (93.1 mm), but similar ( $p=0.0859$ ) to that

produced by placebo IV (17.4 mm). Likewise simulated IV Troxyca ER resulted in a mean oxycodone  $AUC_{0-2hrs}$  (12.35 hrs\*mm) that was significantly lower than that produced by Oxycodone HCl 20 mg IV (133.76 h\*mm), but similar to that produced by IV placebo (2.58 hrs\*mm).

Table 17. Descriptive Summary of Primary Endpoint of Unipolar High VAS – Completer Population (N=29) (Source: CDER Office of Biostatistics and from Table 17 on page 81 of the Full Clinical Study Report for Protocol B4981002)

| Primary Endpoints of High VAS        | Placebo       | Simulated Troxyca ER 20 mg/2.4 mg IV | Oxycodone HCl 20 mg IV |
|--------------------------------------|---------------|--------------------------------------|------------------------|
| <b>E<sub>max</sub></b> (mm)          |               |                                      |                        |
| Mean (SE)                            | 3.7 (1.63)    | 17.4 (4.53)                          | 93.1 (1.99)            |
| Median                               | 0             | 3                                    | 98                     |
| (Q1,Q3)                              | (0,1)         | (1, 25.5)                            | (88.5, 100)            |
| Range (min,max)                      | (0, 33)       | (0.92)                               | (55, 100)              |
| <b>AUE<sub>0-2hrs</sub></b> (h x mm) |               |                                      |                        |
| Mean (SD)                            | 2.58 (6.41)   | 12.34 (27.15)                        | 133.76 (37.30)         |
| Median                               | 0.00          | 2.79                                 | 136.00                 |
| (Q1,Q3)                              | (0.00, 0.83)  | (0.33, 9.50)                         | (117.83, 154.67)       |
| Range (min, max)                     | (0.00, 28.67) | (0.00, 139.54)                       | (47.33, 189.83)        |

#### Percentage Reduction Analysis for E<sub>max</sub> of High VAS

Among 29 completers, approximately 3% (1) of subjects did not have any reduction in E<sub>max</sub> of High following simulated Troxyca ER 20 mg IV treatment compared to Oxycodone HCl 20 mg IV treatment. Approximately 93% (27) and 83% (24) of subjects had at least a 50% reduction in E<sub>max</sub> of High following Troxyca ER 20 mg IV treatment compared to Oxycodone HCl 20 mg IV treatment.

#### Conclusions

Overall, the data indicated that I.V. 2.4 mg naltrexone HCl can block the Drug Liking response and most of the High response produced by I.V. 20 mg oxycodone HCl. As evidenced by the pharmacokinetic data, the difference in Drug Liking and High are not due to differences in exposure to oxycodone as reflected by plasma oxycodone C<sub>5min</sub> and by the partial AUC of oxycodone. The 2.4 mg naltrexone HCl and 20 mg oxycodone HCl represents a <sup>(b) (4)</sup> ratio. The data suggest that in the event that Troxyca ER capsule contents are crushed, resulting in release of all the naltrexone, the preparation of a solution for intravenous injection using the crushed Troxyca ER capsule contents will not be effective in producing subjective effects such as Drug Liking or High. Troxyca ER capsules may have a deterrent effect to intravenous abuse when the capsule contents are crushed, due to the ability of the released naltrexone to block the effects of the concomitantly released oxycodone.

What this study does not do is to establish the degree of block of oxycodone HCl Drug Liking and High when the ratio of oxycodone HCl to naltrexone HCl is increased. This is significant considering that results from in vitro studies (Category 1) indicate that under some conditions, oxycodone HCl may be preferentially extracted at higher levels compared to the extraction of naltrexone HCl as determined from percentage of label claim extracted. Naltrexone is acting via a competitive opioid receptor blockade to attenuate Drug Liking and High produced by oxycodone HCl administered IV. It is possible that with higher levels of oxycodone HCl compared to levels of naltrexone HCl, the competitive blockade would be partially overcome thereby allowing greater expression of Drug Liking and High following oxycodone HCl administration IV.

## 4.2 Adverse event profile through all phases of development

The Troxyca ER clinical development program consisted of 14 clinical studies; 2 Phase 3 studies, 5 naltrexone dose ratio/abuse potential studies, and 7 clinical pharmacology/PK studies.

- The to-be-marketed pellet formulation of ALO-02 was administered in 8 studies; 2 Phase 3 studies (B4531001 and B4531002), 2 abuse potential studies (B4531008 and B4531009), and 4 clinical pharmacology/PK studies (B4531003, B4531004, B4531006, and B4531007).
- Commercially available oxycodone HCl alone or in combination with naltrexone HCl was administered in two naltrexone/oxycodone ratios/abuse potential studies, ALO-02-07-201 (4% - 20%) and ALO-02-09-2001 (12% - 24%). In an intravenous (IV) abuse potential study (B4981002), a combination of oxycodone HCl and 12% naltrexone HCl (to simulate IV administration of crushed ALO-02) was administered.
- A pilot or prototype formulation of ER oxycodone HCl and sequestered naltrexone HCl was administered in 3 clinical pharmacology/PK studies (ALO-02-07-102, ALO-02-08-103, and ALO-02-09-1001).

An examination of the Integrated Summary of Safety (ISS) reveals that during the clinical development program for Troxyca ER Capsules a total of 59 subjects reported euphoric mood as an adverse effect. Fifty-eight of the 59 subjects reported euphoric mood during the two naltrexone dose ratio/abuse potential studies. These two studies did not use the to-be-marketed formulation of Troxyca ER capsules but were pilot studies intended to determine the ratio of oxycodone HCl to naltrexone HCl, both commercially available, to be used in the final to-be-marketed formulation of Troxyca ER capsules. The one additional subject reporting euphoric mode was involved in a Phase 1 pharmacokinetic study. Euphoric mood was not reported in either of the Troxyca ER or Placebo groups in the 2 Phase 3 studies (Studies B4531001 and B4531002).

“Feeling abnormal” only occurred in 1 of the Phase 3 study subjects and 1 subject from clinical pharmacology/PK study subjects using Troxyca ER capsules.

## 4.4 Evidence of abuse, misuse and diversion in clinical trials

Withdrawal syndrome, drug withdrawal syndrome, drug abuse, drug dependence, mood altered, and intentional drug misuse only occurred in the Phase 3 study subjects.

The following two Phase 3 studies (totaling 805 subjects) were conducted using Troxyca ER capsules.

- Study B4531001 was a multicenter, 12-month, open-label, single-arm, safety study of Troxyca ER capsules (oxycodone HCl 20-160 mg/naltrexone HCl 12% of the mg amount of oxycodone HCl) in 395 subjects with moderate-to-severe chronic non-cancer pain of at least 3 months duration requiring a continuous around-the-clock opioid analgesic for an extended period of time.
- Study B4531002 was a multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 capsules (oxycodone HCl 20-160 mg/naltrexone HCl 12% of the mg amount of oxycodone HCl) in 410 subjects with moderate-to-severe chronic lower back pain. The total duration of treatment was 18 to 20 weeks, including a 4- to 6-week open-label conversion and titration period followed by a 12-week double-blind treatment period and a 2-week double-blind post-treatment period. At the end of the open-label conversion and titration period, subjects who responded to and tolerated treatment were randomized to ALO-02 or placebo.

Out of 805 subjects participating in the Phase 3 studies (B4531001 and B4531002):

- Drug abuse was reported in one subject from study B4531001. Subject was removed from the study.
- Drug dependence as reported in one subject from study B4531001.
- “Mood altered” was reported in one subject from study B4531001.
- Intentional drug misuse was reported in one subject from study B4531002 and subject was removed from study. The Investigator commented that this event of intentional drug misuse was drug diversion and the subject was not taking the study drug as prescribed.
- 1 Drug diversion case noted during study B4531001.

With regard to documentation of withdrawal as measured by COWS scores in study B4531001

- 342 Troxyca ER subjects had maximum COWS scores of <5 indicating little or no withdrawal
- 52 Troxyca ER subjects had maximum COWS scores of 5-12, indicating mild withdrawal
- 1 Troxyca ER subject had COWS score 25-36, indicating moderately severe withdrawal.

During the titration period of Study B4531002:

- 363 (96.8%) Troxyca ER subjects displayed no withdrawal (COWS score <5)
- 12 (3.2%) Troxyca ER subjects displayed mild withdrawal (COWS score 5-12)
- No subjects had COWS above  $\geq 13$

During the double-blind treatment period of study B4531002

- 133 (95%) of Troxyca ER subjects displayed no withdrawal (COWS score <5)
- 7 (5%) of Troxyca ER subjects displayed mild withdrawal (COWS score 5-12)

## 5. Regulatory issues and assessment

Due to containing oxycodone, Troxyca ER capsules are in Schedule II of the federal Controlled Substances Act.

Sponsor is proposing to add to Section 9.2 of the label under “In Vitro Testing” the statement: “When TROXYCA ER is crushed and mixed in a variety of solvents, both oxycodone HCl and naltrexone HCl

are simultaneously extracted.” This statement is supported by the in vitro studies and should be accepted in the label.

Sponsor is proposing to place into Section 9.2 of the label descriptions including results of oral study B4531008 and intranasal study B4531009. These studies do provide support for deterrent effects of crushed Troxyca ER to oral and intranasal abuse and should be allowed in the label. With respect to oral study B4531008 Sponsor further proposes to document the effects of intact Troxyca ER in relation to the comparator (IR Oxycodone HCl crushed). [REDACTED] (b) (4)  
[REDACTED]

Sponsor also provided a brief description of simulated intravenous study B4981002. This study did provide evidence that the presence of 12% naltrexone in the Troxyca ER formulation can block subjective effects of the available oxycodone assuming all naltrexone is released as is the case with crushing Troxyca ER contents. As such, description of this study in the label is acceptable.

## **6. Other relevant information**

Troxyca ER Capsules has not previously been marketed in the United States or other countries.

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/s/  
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JAMES M TOLLIVER  
09/16/2015

SILVIA N CALDERON  
09/16/2015

MICHAEL KLEIN  
09/16/2015

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

Date: September 15, 2015

To: Diana Walker, Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
  
Sharon Hertz, MD, Director - DAAAP

From: Koungh 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 207621  
Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride)  
Extended-release Capsule  
Professional Labeling Review

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As requested in DAAAP's consult dated January 2, 2015, OPDP has reviewed the substantially complete prescribing information for Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) Capsules. The substantially complete prescribing information was provided to OPDP on August 31, 2015, via email by Diana Walker with the file name "\\fdsfs01\ODE2\DAAAP\NDA and sNDA\NDA 207621 (Troxyca ER\_Pfizer)\Labeling".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made comments on pages 11 and 26.

We have no comments on the carton/container labeling submitted in the original submission dated December 19, 2014.

Please note that our comments on the PPI were provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP) on September 14, 2015.

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](mailto:Koung.Lee@fda.hhs.gov).

(b) (4)



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/s/  
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KOUNG U LEE  
09/15/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: September 14, 2015

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

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)

Drug Name (established name): TROXYCA ER ( oxycodone hydrochloride and naltrexone hydrochloride)

Dosage Form and Route: extended-release capsules, for oral use, CII

Application Type/Number: 207621

Applicant: Pfizer Inc.

## 1 INTRODUCTION

On December 19, 2014, Pfizer Inc. submitted for the Agency's review a New Drug Application (NDA) 207621 for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules. The proposed indication for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) 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 2, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules.

## 2 MATERIAL REVIEWED

- Draft TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules MG received on December 19, 2014, and received by DMPP and OPDP on August 31, 2015.
- Draft TROXYCA ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules Prescribing Information (PI) received on December 19, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 31, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> 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 document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is 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 is 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.

Please let us know if you have any questions.

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/s/  
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MORGAN A WALKER  
09/14/2015

KOUNG U LEE  
09/14/2015

BARBARA A FULLER  
09/14/2015

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY (CIS)**

DATE: September 11, 2015

TO: Diana Walker, Regulatory Project Manager  
Elizabeth Kilgore, M.D., Medical Officer  
Joshua Lloyd, 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  
Susan Thompson, M.D., Team Leader, for  
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 207621

APPLICANT: Pfizer, Inc.

DRUG: Oxycodone and Naltrexone (Troxyca<sup>®</sup>) Extended Release Capsules

NME: No

INDICATION: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, for which alternative treatment options are inadequate

REVIEW CLASSIFICATION: Standard

APPLICATION SUBMISSION DATE: December 19, 2014

DARRTS CONSULTATION DATE: February 26, 2015

DARRTS CIS GOAL DATE: September 14, 2015

REGULATORY ACTION GOAL DATE: October 19, 2015

PDUFA DUE DATE: October 19, 2015

## I. BACKGROUND

In this 505(b)(2) NDA for Troxyca<sup>®</sup> (trade name pending approval), Pfizer, Inc. (**Pfizer**) references Roxycodone<sup>®</sup> (oxycodone, approved in 2000) and Revia<sup>®</sup> (naltrexone, approved in 1984) to support the marketing approval of an extended-release capsule formulation of oxycodone engineered for abuse-deterrence using naltrexone (opioid antagonist). The naltrexone component of Troxyca<sup>®</sup> remains sequestered and unavailable for systemic absorption, unless the capsule is manipulated (e.g., crushing) to release it for immediate mitigation of oxycodone effect.

In the United States (US), the therapeutic use of opioids appears to have increased since 1997, as indicated by the nearly ten-fold increase in the sales of hydrocodone and oxycodone, presumably for the management of chronic pain. With the increasing sales of opioids, their illicit use (drug abuse and/or diversion) appears to have also increased: according to a 2009 US survey, over two million users of prescription pain relievers in 2008 were new opioid abusers, an estimate similar to the number of new marijuana and/or cigarette users for that year.

Troxyca<sup>®</sup> is intended to be used as an extended-release (**ER**), abuse-deterrent opioid analgesic for the management of pain severe enough to require daily, around-the-clock (**ATC**), long-term opioid treatment, for which alternative treatment options are inadequate. Of the original studies sponsored by Pfizer (under IND 107037), Studies B4531002 and B4531009 were selected for on-site audit (as core efficacy and human abuse liability studies, respectively) at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites with large subject enrollment and/or analgesic efficacy effect size. The two studies are outlined below (study medication referred to as ALO-02).

### **Study B4531002**

*A Multicenter, 12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Determine the Efficacy and Safety of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride) Extended-Release Capsules in Subjects with Moderate-to-Severe Chronic Low Back Pain*

This double-blind, placebo-controlled, randomized withdrawal study was conducted between June 2012 and June 2013 in 281 randomized subjects with chronic low back pain (**CLBP**) at 42 US clinical investigator (**CI**) sites. The primary study objective was to determine the analgesic efficacy of ALO-02 relative to placebo in subjects with moderate/severe CLBP requiring continuous opioid analgesia.

The study consisted of four study periods: (1) screening, up to two weeks; (2) open-label conversion and dose titration, up to six weeks; (3) baseline evaluation, randomization, and 12 weeks of blinded treatment or withdrawal; and (4) dose-taper and follow up, two weeks. Only those subjects achieving a satisfactory treatment response during open-label dose titration were randomized to continue into the blinded study, either on the same study drug (and dose) or switched to placebo.

### **Subject Selection**

- Adults (age  $\geq 18$  years) with non-specific moderate/severe CLBP for over three months, daily numerical rating scale (**NRS**) pain score  $\geq 5$  and  $\leq 9$ , requiring continuous extended opioid analgesia
- Non-specific CLBP: location of back pain between last thoracic vertebra and lower gluteal folds, with or without radiation into thigh, Classification 1 or 2 per Quebec Task Force on Spinal Disorders
- Continuous extended opioid analgesia: CI discretion, extended requirement ( $\geq$  four of last seven days) for oxycodone (or equivalent) at doses of up to 160 mg/day

### **Exclusion Criteria**

- CLBP due to specific conditions, including cancer/tumor, infection, surgery/trauma, vertebral compression, Paget's disease of the spine, osteoarthritis, fibromyalgia, and neuropathic pain syndrome

- Conditions that increase risk or interfere with results interpretation, including pregnancy, lactation, inability to reliably use effective contraception, and body mass index (**BMI**) > 40 kg/m<sup>2</sup>
- On-going alcohol or drug abuse or a documented significant history of prior alcohol or drug abuse, positive urine drug test for illicit drug substances or unexpected drug substances (other than those reported as therapeutic concomitant medications)
- Within last two years: lumbosacral radiculopathy, spinal stenosis with neurologic impairment and/or neurogenic claudication
- Within last one year: hospitalization for depression or suicide attempt, suicidal ideation and/or behavior in the last year based on Sheehan-Suicidality Tracking Scale (**S-ST**S)
- Within last two to six months: back surgery or major trauma (within six months), nerve/plexus block including epidural corticosteroids (within three months), major surgery (within two months)

### Treatment Groups and Regimen

- *Open-label conversion to ALO-02 and dose titration:* Total daily oxycodone dose of 20-160 mg (20, 40, 60, 80, 100, 120, 140, or 160), divided doses twice daily 12 hours apart, capsule to be swallowed whole without chewing or dissolving
- *Randomization and treatment withdrawal:* For subjects qualified with acceptable open-label treatment response (dose unchanged over at least last seven consecutive days), randomization in equal ratio to ALO-02 or placebo, randomization stratified by previously used analgesic, opioid or non-opioid
- Study medication taper (or dummy taper) to avoid opioid withdrawal during first two weeks of blinded treatment and at treatment completion
- Rescue medications (daily e-diary): acetaminophen ≤ 3.0 g/day as needed (anytime) and/or immediate-release single-ingredient oxycodone (open-label Weeks 1-3)
- Permitted therapies: non-scheduled concomitant medications (including pre-study anti-emetics and bowel regimen) and stable physical therapy (including heat treatment)
- Prohibited therapies: opioid analgesics (including tramadol, tapentadol, and buprenorphine), monoamine oxidase inhibitors, and
  - Any non-opioid adjunctive analgesics (including pregabalin and tricyclic antidepressants) and non-steroidal anti-inflammatory drugs (**NSAIDs**) to manage pain (non-pain indications permitted)
  - Any procedures (e.g., nerve blocks or implantation of spinal cord stimulator) or new non-pharmacological therapies for CLBP
  - Muscle relaxants (including benzodiazepines), topical anesthetics, corticosteroids (epidural, intramuscular, oral, or local) for CLBP management

### Major Endpoints and Analyses

Primary analysis was defined as the change in NRS pain score for ALO-02 relative to placebo from baseline (at randomization) to the final two blinded treatment weeks (Weeks 11 and 12), examined by analysis of covariance (**ANCOVA**) using covariates of treatment group, prior analgesic (opioid or non-opioid), baseline NRS pain score, and total daily ALO-02 dose.

- Primary efficacy endpoint: daily NRS score for CLBP on an 11-point scale (0 = no pain, 10 = worst possible pain), subject self-reporting in e-diary
- Safety: Adverse events (**AEs**), Clinical Opiate Withdrawal Scale (**COWS**), Subjective Opiate Withdrawal Scale (**SOWS**), vital signs, physical exam, laboratory tests, and electrocardiogram (**ECG**)

- Roland-Morris Disability Questionnaire (**RMDQ**): 24-item self-rating of disability due to pain
- Patient Global Assessment (**PGA**): five-point scale, scores of 1 (very good) to 5 (very poor)
- Rescue medication use: recorded at any time by subject in e-diary
- Brief Pain Inventory (**BPI**): impact of pain on daily functioning
- Participant satisfaction rating: five-point scale, scores of 1 (very dissatisfied) to 5 (very satisfied)

### **Sponsor-Reported Outcomes**

- Relative to placebo, blinded ALO-02 treatment resulted in significantly smaller mean change in NRS pain score (result supported by sensitivity/secondary analyses, not attributable to rescue medication).
- The study medication was well tolerated, and the observed safety profile was consistent with other ER opioids in comparable populations. There were no deaths or treatment-related SAEs. Laboratory abnormalities appeared unrelated to either ALO-02 or placebo.

### **Study B4531009**

*A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, 4-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release and Placebo When Administered Intranasally to Non-Dependent Recreational Opioid Users*

This randomized, controlled (placebo and active), double-blind, four-way crossover study was conducted between February and July of 2013 in 32 healthy recreational opioid users randomized at a single CI site in Canada. The primary study objective was to determine the abuse potential of crushed intranasal (**IN**) ALO-02 relative to immediate release (**IR**) oxycodone and placebo.

### **Subject Selection**

- Healthy adult (age 18-55 years), recreational, non-dependent opioid users, with opioid use  $\geq$  10 times within last year and at least once within last eight weeks
- Non-dependent recreational opioid user: according to criteria specified in *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision (DSM-IV-TR)*
- Experienced with opioid insufflation (at least three times within last year), BMI of 17.5 to 30.5 kg/m<sup>2</sup>, body weight  $\geq$  50.0 kg (110 lbs)

### **Exclusion Criteria**

- Substance dependence (including alcohol, excluding caffeine/nicotine) per DSM IV-TR; heavy smoking ( $>$  20 cigarettes/day in last 30 days), use of chewing tobacco/nicotine patch, and/or inability to abstain from smoking for over eight hours; positive urine drug screen (**UDS**)
- Contraindications to opioid use (respiratory depression, asthma, hypercarbia, paralytic ileus); any significant condition (hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or immunologic/allergic); unresolved sleep apnea in the last five years
- Positive serology for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (**HIV**) antibody (HIV-1 or HIV-2); hypersensitivity to opioids including oxycodone, naloxone or naltrexone, and/or lactose; any condition affecting drug absorption
- Any abnormality potentially important and/or relevant to this study, including abnormal intranasal cavity and rhinorrhea; abnormal blood pressure and/or ECG; pregnancy or unacceptable contraception

### **Subject Qualification**

Following screening at Visit 1, subjects were tested at Visit 2 (three days, up to 28 days after Visit 1) for opioid withdrawal (naloxone challenge) and for drug responsiveness and tolerance (drug discrimination).

- **Naloxone Challenge (Visit 2, Day 0):** 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 (COWS score < 5) were seen within 30 seconds, an additional 0.6 mg was given IV within five minutes of the first dose. If no withdrawal signs were seen within five minutes of the second dose, the subject proceeded to be evaluated for drug discrimination.
- **Drug Discrimination (Visit 2, Days 1 and 2):** This screening test was to confirm the subject's ability to distinguish IN oxycodone IR from placebo for euphoric effects (abuse potential). On the day after naloxone challenge (Visit 2, Day 1), fasting subjects were randomly given (double-blinded) either crushed oxycodone IR (30 mg) or crushed lactose tablets (placebo, matched to oxycodone IR for taste and appearance). On the following day (Visit 2, Day 2), the alternate study medication was given. On each day, subjects were evaluated pre-dose and up to five hours post-dose (using selected subjective measures) to determine if the unblinded results support qualification for blinded cross-over treatment:
  - Following oxycodone IR dosing, within two hours (relative to placebo): (1)  $\geq 15$ -point peak increase in visual analog scale (VAS) scores for *Drug Liking* and *Take Drug Again*, and (2)  $\geq 30$ -point peak increase for *High*
  - Following oxycodone IR dosing, peak score  $\geq 65$ : (1) within two hours, for *Drug Liking*, and (2) within five hours, for *Take Drug Again*
  - Following placebo dosing, VAS responses: (1) between 0-10 (inclusive) for *High*, or (2) between 40-60 (inclusive) for *Drug Liking* and *Take Drug Again*

Subjects proceeded into blinded cross-over treatment upon a showing of acceptable: (1) testing results, (2) study medication tolerance (no post-dose vomiting within two hours or sneezing within 30 minutes), and (3) general behavior suggestive of successful study completion.

### Blinded Crossover Treatment

At each of the four blinded crossover treatment visits (three days each for Visits 3, 4, 5, and 6), single doses of the following four IN study medications were given in random order (four-way crossover), with 5-14 days of washout between successive treatments visits:

- Treatment A (placebo matched to ALO-02) and Treatment B (crushed ALO-02)
- Treatment C (placebo matched to oxycodone IR) and Treatment D (crushed oxycodone IR)

Baseline evaluations were performed on Day 0, the study medication was administered on Day 1, and endpoint data were collected on Days 1 and 2. Subjects who received at least one dose of any study medication were evaluated at end-of-study (Visit 7), between three to seven days after the last dose.

### Major Endpoints and Analyses

**VAS for perception of drug effect:** Subjects rated their perception of euphoric drug effect at workstations using Scheduled Measurement System (SMS), a proprietary software (INC Research Toronto) for measuring perceived pharmacodynamic (PD) drug effects. The SMS screens presented various visual scales (VAS) requiring either a unipolar (positive only) or a bipolar (positive or negative) response. The VAS data were plotted to determine the various PD endpoints indicative of abuse potential.

- Co-primary endpoints: (1) mean peak effect ( $E_{max}$ ), and (2) area under the effect curve (AUE) for post-dose Hours 0-2 ( $AUE_{0-2h}$ ), for (a) *Drug Liking* (bipolar VAS), and (b) *High* (unipolar VAS)
- VAS for *Any Drug Effects*, *Good Drug Effects*, *Bad Drug Effects*, *Feel Sick*, *Nausea*, *Sleepy*, and *Dizzy*:  $E_{max}$ ,  $AUE_{0-1h}$ ,  $AUE_{0-2h}$ ,  $AUE_{0-8h}$ , and  $AUE_{0-24h}$ , and time to maximum effect ( $TE_{max}$ )
- $AUE_{0-1h}$ ,  $AUE_{0-8h}$ ,  $AUE_{0-24h}$ ,  $TE_{max}$  for *Drug Liking* and *High*;  $E_{max}$  and mean observed effect ( $E_{mean}$ ) for *Take Drug Again*; and  $E_{max}$  and  $E_{mean}$  for *Overall Drug Liking*

**Pupillometry:** As an objective, sensitive, and reliable measure of opioid action, the pupil diameter was measured (using NeurOptics pupillometer) on the same eye under controlled dim light. The data were plotted to determine  $E_{\max}$ ,  $TE_{\max}$ ,  $AUE_{0-1h}$ ,  $AUE_{0-2h}$ ,  $AUE_{0-8h}$ , and  $AUE_{0-24h}$  for pupil response.

**Safety monitoring:** Safety endpoints consisted of adverse events (AEs), laboratory data, vital signs, electrocardiogram (ECG) and continuous cardiac telemetry, capnography for end-tidal carbon dioxide concentration in expired air ( $EtCO_2$ ), pulse oximetry for hemoglobin oxygen saturation ( $SpO_2$ ), and subject-rated scales for nasal AEs.

- Pulse oximetry: monitored continuously for five hours following dosing during *Drug Discrimination* and continuously for 12 hours following dosing during blinded crossover treatment.
- Nasal AEs: subject rating on six-point scale (0 = no problem, 5 = worst possible) based on five categories: (1) burning, (2) need to blow nose, (3) runny nose or nasal discharge, (4) facial pain/pressure, and (5) nasal congestion

**Pharmacokinetic endpoints:** Blood samples were assayed for oxycodone and naltrexone (and their metabolites) prior to dosing and at 13 post-dose time points up to 24 hours.

Measured data were verified for the following endpoints and subjects. For all other endpoints and subjects, data were verified to support any expanded investigation of initial inspectional findings.

- All subjects: *Drug Liking* and *High*, VAS data for  $E_{\max}$  and  $AUE_{0-2h}$
- 10 subjects (randomly selected): AEs and pupillometry data for  $E_{\max}$ ,  $TE_{\max}$ ,  $AUE_{0-1h}$ , and  $AUE_{0-8h}$

### Major Sponsor-Reported Outcomes

- Abuse potential of crushed ALO-02, relative to crushed oxycodone IR:  $E_{\max}$  and  $AUE_{0-2h}$  for *Drug Liking* and *High* were significantly lower, consistent with reduced abuse potential.
- Abuse potential of crushed ALO-02, relative to placebo: Except for *Drug Liking*,  $E_{\max}$  and  $AUE_{0-2h}$  values were significantly greater, consistent with greater abuse potential.
- Results up to 24 hours post-dose for the secondary endpoints *Take Drug Again* and *Overall Drug Liking* were consistent with those for the primary endpoint.
- Crushed ALO-02, relative to crushed oxycodone IR: Oxycodone bioavailability was 20% lower, likely due to formulation differences. Naltrexone was apparently absorbed rapidly and blocked opioid receptors to mitigate oxycodone activity.
- Safety of crushed ALO-02, relative to crushed oxycodone IR: Fewer AEs were observed, particularly those related to opioid activity (euphoria, nausea, somnolence). All treatments were well tolerated and SAEs or deaths were not observed.

## II. INSPECTIONS

In auditing Studies B4531002 and B4531009, three CI sites were selected for GCP inspection based on the following NDA review considerations:

- Site 1060: Largest number of subjects screened and randomized for Study B4531002
- Site 1028: Largest site-specific treatment effect seen for Study B4531002
- Site 1001: Only CI site for Study B4531009, to evaluate human abuse liability (HAL)

For either study, no special review concerns were identified regarding CI conflict of interest or study conduct, including protocol adherence, protocol violations, safety monitoring, or AE reporting. The results of the three inspections are shown below:

| Clinical Investigator |   | Study, Site, Enrollment                                      | Inspection Outcome                             |
|-----------------------|---|--|--|
| 1                     | David W. Bouda, M.D.<br>Heartland Clinical Research, Inc.<br>2201 North 90 <sup>th</sup> Street, Suite 126<br>Omaha, NE 68134 | Study B4531002<br>Site 1060<br>30 randomized<br>23 completed | April 27 – May 1, 2015<br>NAI                  |
| 2                     | Standiford Helm, M.D.<br>Pacific Coast Pain Management Center<br>24902 Moulton Parkway, Suite 200<br>Laguna Hills, CA 92637   | Study B4531002<br>Site 1028<br>6 randomized<br>4 completed   | May 18 - 28, 2015<br>NAI                       |
| 3                     | Pierre Geoffroy, M.D.<br>INC Research Toronto Inc.<br>720 King Street West, 7th Floor<br>Toronto, Canada ON M5V 2T3           | Study B4531009<br>Site 1001<br>32 randomized<br>28 completed | June 15 - 19, 2015<br>Pending, preliminary NAI |

NAI = no action indicated (no significant violations); Pending = preliminary communication with field investigator

### 1. David W. Bouda, 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 (randomization, efficacy, AEs, protocol deviations, and subject discontinuations)

#### b. General observations and comments:

Study B4531002, Site 1060: 58 were screened, 30 were enrolled and all 30 were randomized, and 23 completed the study. Five randomized subjects were withdrawn, three for lack of efficacy and two for using prohibited medications. Two randomized subjects were lost to follow-up. Case records were reviewed for all enrolled subjects, including complete review for 11 subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including IRB/sponsor oversight of study conduct. Records were well maintained and all audited data were verifiable among source records, case report forms (**CRFs**), and data listings.

#### c. Assessment of data integrity: The data from this study site appear reliable.

### 2. Standiford Helm, 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 (randomization, efficacy, AEs, protocol deviations, and subject discontinuations)

b. General observations and comments:

Study B4531002, Site 1028: Seven subjects were screened, six were enrolled and all six were randomized, and four completed the study. Two randomized subjects were withdrawn due to lack of efficacy. Case records were reviewed in detail for all subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including IRB/sponsor oversight of study conduct. Records were well maintained and all audited data were verifiable among source records, CRFs, and data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

**3. Pierre Geoffroy, 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, and data verification (randomization, major efficacy endpoints, AEs, protocol deviations, and subject discontinuations)

b. General observations and comments:

Study B4531009, Site 1001: 130 subjects were screened, 45 were enrolled, 32 were randomized, and 28 completed the study (4 discontinued for positive UDS). Case records were reviewed for all subjects, including detailed review for 10 randomized subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. A minor observation (about informed consent lacking reference to FDA review) was verbally discussed. Study conduct appeared adequate, including IRB/sponsor oversight of study conduct. Records were well maintained and all audited data were verifiable among source records, CRFs, and 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**

Pfizer submitted this NDA 207621 for Troxyca<sup>®</sup>, a new capsule formulation of oxycodone and naltrexone engineered for abuse-deterrent long-term pain management. The NDA was submitted as a 505(b)(2) application based on the reference listed drugs Roxicodone<sup>®</sup> (oxycodone) and Revia<sup>®</sup> (naltrexone). Of the new studies sponsored by Pfizer, two were audited at GCP inspections of three CI sites with large subject enrollment and/or analgesic efficacy effect size.

- Study B4531002 (core efficacy study) was a double-blind, placebo-controlled, randomized withdrawal study conducted between 2012 and 2013 in 281 randomized subjects with CLBP at 42 US CI sites. Open-label dose titration preceded randomization into 12 weeks of blinded maintenance treatment or treatment withdrawal. At Sites 1060 (largest) and 1028 (largest treatment effect), a combined total of 36 subjects were randomized (13%), of whom case records for all subjects were reviewed, including detailed review for 17 subjects (6%).
- Study B4531009 (HAL study) was a randomized, controlled (placebo and active), double-blind, four-way crossover study conducted in 2013 in 32 healthy volunteers (recreational opioid users) randomized at the single inspected CI site in Canada. Case records for all subjects were reviewed, including detailed review for 10 randomized subjects (31%).

For all three CI sites, no significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including sponsor monitoring and IRB oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three CI sites appear reliable as reported in the NDA.

Note: For Site 1001 (Geoffroy) in Study B4531009, the EIR has not been received from the field office and the final inspection outcome remains pending. Upon receipt and review of the EIR, an addendum to this CIS will be forwarded to the review division if the final outcome changes from that reported in this CIS. Close-out correspondence (with CI, copied to review division) otherwise indicates EIR review completion without new significant findings and inspection outcome finalization as reported in this CIS.

{See appended electronic signature page}

John Lee, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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For:

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Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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/s/  
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JONG HOON LEE  
09/11/2015

JANICE K POHLMAN  
09/11/2015

SUSAN D THOMPSON  
09/11/2015

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## 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\*\*\***

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|                                       |  |
|---------------------------------------|--|
| <b>Date of This Review:</b>           | April 29, 2015   |
| <b>Requesting Office or Division:</b> | Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)  |
| <b>Application Type and Number:</b>   | NDA 207621   |
| <b>Product Name and Strength:</b>     | Troxyca ER<br>(oxycodone hydrochloride and naltrexone hydrochloride)<br>Extended-release capsules<br>10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg,<br>40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg |
| <b>Product Type:</b>                  | Multi-Ingredient   |
| <b>Rx or OTC:</b>                     | Rx   |
| <b>Applicant/Sponsor Name:</b>        | Pfizer Inc.  |
| <b>Submission Date:</b>               | December 19, 2014  |
| <b>OSE RCM #:</b>                     | 2014-2595  |
| <b>DMEPA Primary Reviewer:</b>        | James Schlick, RPh, MBA  |
| <b>DMEPA Team Leader:</b>             | Vicky Borders-Hemphill, PharmD   |

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## 1 REASON FOR REVIEW

As part of the approval process for Troxyca ER, DAAAP requested that we review proposed container labels and package insert labeling for areas that may lead to medication errors.

## 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.

| <b>Table 1. Materials Considered for this Label and Labeling Review</b> |   |
|---|---|
| <b>Material Reviewed</b>  | <b>Appendix Section (for Methods and Results)</b> |
| Product Information/Prescribing Information                             | A   |
| Previous DMEPA Reviews  | N/A B   |
| Human Factors Study   | N/A C   |
| ISMP Newsletters  | N/A D   |
| FDA Adverse Event Reporting System (FAERS)*                             | N/A E   |
| Other   | N/A F   |
| Labels and Labeling   | G   |

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

We reviewed the proposed container labels and compared them to Pfizer's Embeda label as they appear similar to the proposed Troxyca ER container label. Pfizer had redesigned the Embeda labels in 2013 and we reviewed them in OSE# 2013-1583. We evaluated the similar location of the Pfizer logo at the top of the label, the Medication Guide statement, and the presentation of the proprietary name in all caps. We determined that the proposed container labels, prescribing information and medication guide are acceptable from a medication error perspective.

## 4 CONCLUSION & RECOMMENDATIONS

We find the proposed container labels, prescribing information, and medication guide to be acceptable from a medication error perspective. We have no recommendations at this time.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Troxyca ER that Pfizer submitted on December 19, 2014.

| <b>Table 2. Relevant Product Information for Troxyca ER</b> |   |
|---|---|
| <b>Initial Approval Date</b>                                | N/A   |
| <b>Active Ingredient</b>                                    | oxycodone hydrochloride and naltrexone hydrochloride  |
| <b>Indication</b>   | (b) (4)   |
| <b>Route of Administration</b>                              | Oral  |
| <b>Dosage Form</b>  | Extended-release capsule  |
| <b>Strength</b>   | 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg,<br>40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg   |
| <b>Dose and Frequency</b>                                   | 20 mg to 160 mg per day in two divided doses every 12 hours. Swallowed whole or the contents of the capsules sprinkled on apple sauce |
| <b>How Supplied</b>   | each strength in bottles of 100 capsules  |
| <b>Storage</b>  | 25°C (77°F), with excursions permitted to 15 to 30°C (59-86°F)  |
| <b>Container Closure</b>                                    | high density polyethylene (HDPE) bottles with (b) (4)<br>(b) (4) child resistant screw cap  |

## **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,<sup>1</sup> along with postmarket medication error data, we reviewed the following Troxyca ER labels and labeling submitted by Pfizer Inc. on December 19, 2014.

- Container label
- Prescribing Information (no image)
- Medication Guide (no image)

### **G.2 Label Images**

(b) (4)



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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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/s/  
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JAMES H SCHLICK  
04/29/2015

BRENDA V BORDERS-HEMPHILL  
04/29/2015

## CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 207621

Applicant: Pfizer

Filing Date: February 17, 2015

Drug Name: Troxyca ER Capsules

IND Number: 107037 (b) (4)

Oxycodone HCl/Naltrexone

Capsules (ALO-02)

| Checklist  | Yes | No | NA | Comment   |
|--|-----|----|----|---|
| What is the regulatory history of this application?  |     |    |    | Developed under two INDs. For IND 107037 – two by Tolliver (DARRTS, 04/16/10 and 07/19/12) and two by Ling Chen (DARRTS 6/27/12 and 11/21/12). (b) (4)  |
| <b>Abuse potential assessment is required if any of the following are true for a drug<sup>12</sup>:</b>  |     |    |    |   |
| 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   |    |    |   |
| <b>Is the drug a new molecular entity?</b>   |     | x  |    |   |
| <b>Is this a new or novel drug formulation?</b>  |     | x  |    |   |
| <b>Content of NDA abuse potential section:</b>   |     |    |    |   |
| <i>Module 1: Administrative Information and Prescribing Information</i>  |     |    |    |   |
| <b>1.11.4 Multiple Module Information Amendment contains:</b>  |     |    |    |   |
| <ul style="list-style-type: none"> <li>A summary, interpretation, and discussion of abuse potential data provided in the NDA.</li> </ul>   | x   |    |    | Two page document provides links to 3 HAP studies and to Module 2 summaries of in vitro data  |
| <ul style="list-style-type: none"> <li>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.</li> </ul> |     | x  |    | No table of contents. No links to in vitro studies or to ISS document.  |
| <ul style="list-style-type: none"> <li>A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA</li> </ul>  | x   |    |    | In two page document Sponsor notes that following an evaluation of the eight factors used to determine scheduling of opioids listed in 21 U.S.C. 811(c), it is concluded that Troxyca ER should be in Schedule II of the Controlled Substances Act. |
| <i>Module 2: Summaries</i>   |     |    |    |   |
| <b>2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.</b>  |     |    |    |   |
|  |     | x  |    | Under Module 2.3.P.2 there is a summary of the in vitro data. No  |

1 21 CFR 314.50(d)(5)(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 overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(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

| Checklist   | Yes | No | NA | Comment   |
|---|-----|----|----|---|
|   |     |    |    | other nonclinical studies are noted   |
| <b>Module 3: Quality</b>  |     |    |    |   |
| 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 manipulation). | x   |    |    |   |
| Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?   | x   |    |    | Yes. 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.  |
| 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.                                 |     |    |    |   |
| Is this an extended release or abuse-resistant formulation?   | x   |    |    | It is an extended release and abuse-resistant formulation.  |
| <b>Module 4: Nonclinical Study Reports</b>  |     |    |    |   |
| 4.2.1 Pharmacology  |     | x  |    |   |
| 4.2.1.1 Primary Pharmacodynamics - contains study reports ( <i>in vitro</i> and <i>in vivo</i> ) describing the binding profile of the parent drug and all active metabolites.  |     | x  |    |   |
| Are <i>in vitro</i> receptor binding studies included?  |     | x  |    |   |
| Are functional assays included?   |     | x  |    |   |
| 4.2.3.7.4 Dependence – section includes:  |     |    |    |   |
| <ul style="list-style-type: none"> <li>• A complete discussion of the nonclinical data related to abuse potential.</li> <li>• Complete study reports of all nonclinical abuse potential studies.</li> </ul>               |     | x  |    |   |
| <b>Animal Behavioral and Dependence Pharmacology:</b> 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.   |
| 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  |    |   |
| <b>Module 5: Clinical Study Reports</b>   |     |    |    |   |
| 5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.  |     |    |    |   |
| <b>Human abuse potential study:</b>   |     |    |    |   |
| Was a human abuse potential study conducted?  | x   |    |    | There are three HAP studies<br>1) <b>Oral HAP Study B4531008</b> - A randomized, double-blind, double-dummy, placebo-controlled, single-dose, 6-way Crossover study to determine the relative abuse potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) compared to oxycodone immediate-release and placebo when administered orally to non-dependent, recreational opioid users<br>2) <b>Intranasal HAP Study</b> |

## CSS Filing Checklist for NDA/BLA or Supplement

| Checklist  | Yes | No | NA | Comment   |
|--|-----|----|----|---|
|  |     |    |    | <p><b><u>B4531009</u></b> - •A randomized, double-blind, placebo-controlled, single-dose, 4-way crossover study to determine the relative abuse potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) compared to oxycodone immediate-release, and placebo when administered intranasally to non-dependent, recreational opioid users.</p> <p>3) <b><u>Simulated Intravenous HAP Study B4981002</u></b> - A randomized, single-dose, placebo-controlled, double-blind, 3-way crossover study to determine the relative abuse potential of intravenous oxycodone hydrochloride alone or in combination with intravenous naltrexone hydrochloride in opioid experienced non-dependent subjects</p> <p>For all three HAP studies appropriate pharmacodynamic and pharmacokinetic measures and parameters were used.</p> |
| Are all the primary data included in the NDA?  | x   |    |    |   |
| Is a Statistics consult necessary?   | x   |    |    | Yes. CSS provided a statistical consult request to Office of Biostatistics for review of the three HAP studies in NDA 207621(DARRTS, January 8, 2015)   |
| <b>Other Clinical trials:</b>  |     |    |    |   |
| Is there evidence of drug accountability issues or overt evidence of misuse, abuse, or diversions?   | x   |    |    | Diversion was seen in one phase 3 trial.  |
| Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]? | x   |    |    | Information is provided in the Integrated Summary of Safety under Module 5.3.5.3. Drug abuse was reported in one subject in one Phase 3 trial. Drug dependence was reported for one subject form each of the two Phase 3 studies. Intentional drug misuse with drug diversion was reported for one subject in one Phase 3 trial.  |
| Does Compliance need to be consulted re: site inspection for data integrity or other issues?   |     | x  |    |   |
|  |     |    |    |   |
|  |     |    |    |   |

## CSS Filing Checklist for NDA/BLA or Supplement

| Checklist  | Yes | No | NA | Comment  |
|--|-----|----|----|--|
| 5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product |     |    |    |  |
| Did you review the scientific literature?  |     | x  |    | Troxyca ER has not previously been marketed in the U.S. or other countries.                              |
| Did you conducted a search of databases and other information related to misuse, abuse, and addiction?   |     | x  |    |  |
| <b>Is there evidence for any of the following:</b>   |     |    |    |  |
| Accidental overdose in the patient population and vulnerable populations   |     | x  |    |  |
| Overdose associated with misuse and abuse  |     | x  |    |  |
| Unintended pediatric exposures to product  |     |    | NA |  |
| <b>Labeling issues</b>   |     |    |    |  |
| Drug disposal issues?  |     |    | NA |  |
| <b>Postmarketing activities [PMRs, PMCs, REMS]</b>   |     |    |    |  |
|  | x   |    |    | REMS   |
| <b>Scheduling activities</b>   |     |    |    |  |
|  |     |    |    | According to Sponsor, Troxyca ER containing oxycodone is in Schedule II of the Controlled Substance Act. |

Is NDA FILEABLE from a CSS perspective? Yes, contingent to correcting deficiencies below.<sup>3</sup>

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.**

Deficiencies are listed below.

Module 1.14.4 should have a link to a table of contents having links to all nonclinical and clinical studies related to determining abuse potential. There is no link to the in vitro abuse (Category 1) abuse deterrent studies or to the Integrated Summary of Safety sections dealing with abuse, diversion, and withdrawal documented in the clinical study program.

Provide the “Dosage and Administration Instructions (DAI)” and “Pharmacy Manual” for each of the human abuse potential studies B4531008, B4531009, and B4531002. If these documents are part of the NDA submission, provide their location.

<sup>3</sup> Manual of Policies and Procedures: Center for Evaluation and Research; Policy and Procedures; Office of New Drugs; Good Review Practice: Refuse to File.  
<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm370948.htm>

## CSS Filing Checklist for NDA/BLA or Supplement

CSS Reviewer: James M. Tolliver, Ph.D.

Date: 02/11/2015

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Team Leader: Silvia Calderon, Ph.D.

Date: 02/11/2015

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/s/  
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JAMES M TOLLIVER  
02/11/2015

SILVIA N CALDERON  
02/11/2015

MICHAEL KLEIN  
02/11/2015

# 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:** NDA 207621

**Application Type:** New NDA, Type 3/4

**Name of Drug/Dosage Form:** Troxyca ER [ALO-02 (Oxycodone hydrochloride and naltrexone hydrochloride)] Capsules, 10mg, 20mg, 30mg, 40mg, 60mg, 80mg

**Applicant:** Pfizer, Inc

**Receipt Date:** December 19, 2014

**Goal Date:** October 19, 2015

## 1. Regulatory History and Applicant's Main Proposals

Troxyca ER is a combination opioid analgesic (oxycodone) + sequestered opioid antagonist (naltrexone). The Sponsor's detailed regulatory history and meeting minutes can be found under IND 107037. This will be a 505(b)(2) application referencing Roxicodone and Revia. The Sponsor requested Priority Review based on their proposed abuse-deterrent (AD) formulation, however it will not be granted as the Sponsor did not conduct head-to-head studies with the previously approved AD formulation.

## 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. The only deficiency identified was #2, the length of Highlights exceeded one-half page. A waiver for this requirement will be discussed in the Division and the recommendation conveyed to the applicant in the 74-day letter.

## 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.

## Selected Requirements of Prescribing Information

### Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 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:**

- 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:** *Highlights is longer than one-half page and also contains a Boxed Warning.*

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

**Comment:**

- YES** 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:**

- YES** 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:**

- YES** 7. Section headings must be presented in the following order in HL:

| Section                           | Required/Optional                                     |
|-----------------------------------|---|
| • Highlights Heading              | Required  |
| • Highlights Limitation Statement | Required  |
| • Product Title                   | Required  |
| • Initial U.S. Approval           | Required  |
| • 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     |

## Selected Requirements of Prescribing Information

|  |          |
|--|----------|
| • 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:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 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:**

#### Highlights Limitation Statement

- YES** 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:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### 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.

**Comment:**

- 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**

## Selected Requirements of Prescribing Information

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

- YES** 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

## Selected Requirements of Prescribing Information

- YES** 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:*

### 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:*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:*

## Selected Requirements of Prescribing Information

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### 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:*
- YES** 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:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

|  |
|--|
| <b>BOXED WARNING</b>   |
| <b>1 INDICATIONS AND USAGE</b>                                   |
| <b>2 DOSAGE AND ADMINISTRATION</b>                               |
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                              |
| <b>4 CONTRAINDICATIONS</b>                                       |
| <b>5 WARNINGS AND PRECAUTIONS</b>                                |
| <b>6 ADVERSE REACTIONS</b>                                       |
| <b>7 DRUG INTERACTIONS</b>                                       |
| <b>8 USE IN SPECIFIC POPULATIONS</b>                             |
| <b>8.1 Pregnancy</b>   |
| <b>8.2 Labor and Delivery</b>                                    |
| <b>8.3 Nursing Mothers</b>                                       |
| <b>8.4 Pediatric Use</b>   |
| <b>8.5 Geriatric Use</b>   |
| <b>9 DRUG ABUSE AND DEPENDENCE</b>                               |
| <b>9.1 Controlled Substance</b>                                  |
| <b>9.2 Abuse</b>   |
| <b>9.3 Dependence</b>  |
| <b>10 OVERDOSAGE</b>   |
| <b>11 DESCRIPTION</b>  |
| <b>12 CLINICAL PHARMACOLOGY</b>                                  |
| <b>12.1 Mechanism of Action</b>                                  |
| <b>12.2 Pharmacodynamics</b>                                     |
| <b>12.3 Pharmacokinetics</b>                                     |
| <b>12.4 Microbiology (by guidance)</b>                           |
| <b>12.5 Pharmacogenomics (by guidance)</b>                       |
| <b>13 NONCLINICAL TOXICOLOGY</b>                                 |
| <b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b> |
| <b>13.2 Animal Toxicology and/or Pharmacology</b>                |
| <b>14 CLINICAL STUDIES</b>                                       |
| <b>15 REFERENCES</b>   |
| <b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>                      |
| <b>17 PATIENT COUNSELING INFORMATION</b>                         |

**Comment:**

- YES** 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:**

## Selected Requirements of Prescribing Information

- N/A** 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

- YES** 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

- YES** 36. In the BW, all text should be **bolded**.

*Comment:*

- YES** 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

- N/A** 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:**

- YES** 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:**

# 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.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

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]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
02/11/2015

PARINDA JANI  
02/11/2015

## 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)]**

| Application Information   |   |  |
|---|---|--|
| NDA # 207621<br>BLA#  | NDA Supplement #: S-<br>BLA Supplement #: S-  | Efficacy Supplement Category:<br><input type="checkbox"/> New Indication (SE1)<br><input type="checkbox"/> New Dosing Regimen (SE2)<br><input type="checkbox"/> New Route Of Administration (SE3)<br><input type="checkbox"/> Comparative Efficacy Claim (SE4)<br><input type="checkbox"/> New Patient Population (SE5)<br><input type="checkbox"/> Rx To OTC Switch (SE6)<br><input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7)<br><input type="checkbox"/> Animal Rule Confirmatory Study (SE7)<br><input type="checkbox"/> Labeling Change With Clinical Data (SE8)<br><input type="checkbox"/> Manufacturing Change With Clinical Data (SE9)<br><input type="checkbox"/> Pediatric |
| Proprietary Name: Troxyca ER<br>Established/Proper Name: ALO-02 (Oxycodone hydrochloride and naltrexone hydrochloride)<br>Dosage Form: Capsule<br>Strengths: 10mg, 20mg, 30mg, 40mg, 60mg, 80mg   |   |  |
| Applicant: Pfizer, Inc<br>Agent for Applicant (if applicable): N/A  |   |  |
| Date of Application: December 19, 2014<br>Date of Receipt: December 19, 2014<br>Date clock started after UN: N/A  |   |  |
| PDUFA Goal Date: October 19, 2015   |   | Action Goal Date (if different): N/A   |
| Filing Date: February 17, 2015  |   | Date of Filing Meeting: January 29, 2015   |
| Chemical Classification (original NDAs only) :<br><input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination<br><input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination<br><input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination<br><input checked="" type="checkbox"/> Type 4- New Combination<br><input type="checkbox"/> Type 5- New Formulation or New Manufacturer<br><input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA<br><input type="checkbox"/> Type 8- Partial Rx to OTC Switch |   |  |
| Proposed indication: Management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate.  |   |  |
| Type of Original NDA:<br>AND (if applicable)<br>Type of NDA Supplement:   | <input type="checkbox"/> 505(b)(1)<br><input checked="" type="checkbox"/> 505(b)(2) Revia and Roxicodone/NDA 018932, NDA 021011<br><input type="checkbox"/> 505(b)(1)<br><input type="checkbox"/> 505(b)(2) |  |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>   |   |  |

|   |   |
|---|---|
| Type of BLA   | <input type="checkbox"/> 351(a)<br><input type="checkbox"/> 351(k)  |
| <b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>   |   |
| Review Classification:  | <input checked="" type="checkbox"/> Standard<br><input type="checkbox"/> Priority   |
| <i>The application will be a priority review if:</i>  | <input type="checkbox"/> Pediatric WR<br><input type="checkbox"/> QIDP<br><input type="checkbox"/> Tropical Disease Priority Review Voucher<br><input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher  |
| <ul style="list-style-type: none"><li>• 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)</li><li>• The product is a Qualified Infectious Disease Product (QIDP)</li><li>• A Tropical Disease Priority Review Voucher was submitted</li><li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li></ul> |   |
| Resubmission after withdrawal? <input type="checkbox"/>   | Resubmission after refuse to file? <input type="checkbox"/>   |
| Part 3 Combination Product? <input type="checkbox"/>  | <input type="checkbox"/> Convenience kit/Co-package<br><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)<br><input type="checkbox"/> Device coated/impregnated/combined with drug<br><input type="checkbox"/> Device coated/impregnated/combined with biologic<br><input type="checkbox"/> Separate products requiring cross-labeling<br><input type="checkbox"/> Drug/Biologic<br><input type="checkbox"/> Possible combination based on cross-labeling of separate products<br><input type="checkbox"/> Other (drug/device/biological product) |
| <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>  |   |

|  |  |
|--|--|
| <input type="checkbox"/> Fast Track Designation<br><input type="checkbox"/> Breakthrough Therapy Designation<br><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i><br><input type="checkbox"/> Rolling Review<br><input type="checkbox"/> Orphan Designation<br><br><input type="checkbox"/> Rx-to-OTC switch, Full<br><input type="checkbox"/> Rx-to-OTC switch, Partial<br><input type="checkbox"/> Direct-to-OTC<br><br>Other: | <input type="checkbox"/> PMC response<br><input type="checkbox"/> PMR response:<br><input type="checkbox"/> FDAAA [505(o)]<br><input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)<br><input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)<br><input type="checkbox"/> 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 Numbers: IND 107037 (b) (4)

| Goal Dates/Product Names/Classification Properties  | YES                                 | NO                       | NA | Comment                              |
|---|-------------------------------------|--------------------------|----|--------------------------------------|
| PDUFA and Action Goal dates correct in tracking system?<br><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    | 10/19/2015 – Standard 10-month clock |
| Are the established/proper and applicant names correct in tracking system?<br><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> |    |                                      |

|   |  |                                     |                          |                |
|---|--|-------------------------------------|--------------------------|----------------|
| <i>system.</i>  | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            | <input type="checkbox"/> |                |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i><br><a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a><br><i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            | <input type="checkbox"/> |                |
| <b>Application Integrity Policy</b>   | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i><br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>   | <input type="checkbox"/>   | <input checked="" type="checkbox"/> |                          |                |
| If yes, explain in comment column.  |  |                                     | XX                       |                |
| If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:   | <input type="checkbox"/>   | <input type="checkbox"/>            | XX                       |                |
| <b>User Fees</b>  | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?   | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            |                          |                |
| <u>User Fee Status</u><br><i>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.</i>   | Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>:</i> )<br><input checked="" type="checkbox"/> Paid<br><input type="checkbox"/> Exempt (orphan, government)<br><input type="checkbox"/> Waived (e.g., small business, public health)<br><input type="checkbox"/> Not required |                                     |                          |                |
| <i>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.</i>   | Payment of other user fees:<br><input checked="" type="checkbox"/> Not in arrears<br><input type="checkbox"/> In arrears   |                                     |                          |                |
| <u>User Fee Bundling Policy</u><br><i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i><br><a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>   | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i><br><input checked="" type="checkbox"/> Yes – NAI in this case<br><input type="checkbox"/> No   |                                     |                          |                |
| <b>505(b)(2)<br/>(NDAs/NDA Efficacy Supplements only)</b>   | <b>YES</b>   | <b>NO</b>                           | <b>NA</b>                | <b>Comment</b> |
| Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). If yes, answer the bulleted   | <input checked="" type="checkbox"/>  | <input type="checkbox"/>            |                          |                |

|  |           |                  |                        |                                     |                                     |                                     |                |
|--|-----------|------------------|------------------------|-------------------------------------|-------------------------------------|-------------------------------------|----------------|
| questions below:   |           |                  |                        |                                     |                                     |                                     |                |
| <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>   |           |                  |                        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |
| <ul style="list-style-type: none"> <li>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)].</li> </ul>  |           |                  |                        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |
| <ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>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.</i></p>                    |           |                  |                        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |
| <ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><i>Check the Electronic Orange Book at:</i><br/> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>  |           |                  |                        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |
| <b>If yes, please list below:</b>  |           |                  |                        |                                     |                                     |                                     |                |
| Application No.  | Drug Name | Exclusivity Code | Exclusivity Expiration |                                     |                                     |                                     |                |
|  |           |                  |                        |                                     |                                     |                                     |                |
|  |           |                  |                        |                                     |                                     |                                     |                |
| <p><i>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.</i></p> |           |                  |                        |                                     |                                     |                                     |                |
| <b>Exclusivity</b>   |           |                  |                        | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b> |
| Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i><br><a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>   |           |                  |                        | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                                     |                |
| <b>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)]?</b>  |           |                  |                        | <input type="checkbox"/>            | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |                |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>   |           |                  |                        |                                     |                                     |                                     |                |
| <b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  |           |                  |                        | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input type="checkbox"/>            |                |
| <b>If yes, # years requested: 3</b>  |           |                  |                        |                                     |                                     |                                     |                |
| <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>  |           |                  |                        |                                     |                                     |                                     |                |

|   |                          |                                     |                                     |  |
|---|--------------------------|-------------------------------------|-------------------------------------|--|
| <b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?  | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |  |
| <b>If yes, did the applicant:</b> (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)?<br><br><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>   | <input type="checkbox"/> | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |  |
| <b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?<br><br><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i><br><br><i>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.</i> | <input type="checkbox"/> | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |  |

| Format and Content   |   |                          |                          |                |
|--|---|--------------------------|--------------------------|----------------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>  | <input type="checkbox"/> All paper (except for COL)<br><input checked="" type="checkbox"/> All electronic<br><input type="checkbox"/> Mixed (paper/electronic)<br><br><input checked="" type="checkbox"/> CTD<br><input type="checkbox"/> Non-CTD<br><input type="checkbox"/> Mixed (CTD/non-CTD) |                          |                          |                |
| <b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>  |   |                          |                          |                |
| <b>Overall Format/Content</b>  | <b>YES</b>  | <b>NO</b>                | <b>NA</b>                | <b>Comment</b> |
| <b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup><br><b>If not, explain (e.g., waiver granted).</b>  | <input checked="" type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/> |                |
| <b>Index:</b> Does the submission contain an accurate comprehensive index?   | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                          |                |
| 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:<br><br><input checked="" type="checkbox"/> legible | <input checked="" type="checkbox"/>   | <input type="checkbox"/> |                          |                |

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

|  |                                     |                          |                                     |                |
|--|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <input checked="" type="checkbox"/> English (or translated into English)<br><input checked="" type="checkbox"/> pagination<br><input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)   |                                     |                          |                                     |                |
| <b>If no, explain.</b>   |                                     |                          |                                     |                |
| <b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                |
| <b>If yes, BLA #</b>   |                                     |                          |                                     |                |
|  |                                     |                          |                                     |                |
|  |                                     |                          |                                     |                |
|  |                                     |                          |                                     |                |
|  |                                     |                          |                                     |                |
|  |                                     |                          |                                     |                |
| <b>Forms and Certifications</b>  |                                     |                          |                                     |                |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> |                                     |                          |                                     |                |
| <b>Application Form</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>  |                                     |                          |                                     |                |
| Are all establishments and their registration numbers listed on the form/attached to the form?   | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Patent Information (NDAs/NDA efficacy supplements only)</b>   | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                |
| <b>Financial Disclosure</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>   |                                     |                          |                                     |                |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>  |                                     |                          |                                     |                |
| <b>Clinical Trials Database</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b> |
| Is form FDA 3674 included with authorized signature?   | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                                     |                |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>   |                                     |                          |                                     |                |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>   |                                     |                          |                                     |                |

| <b>Debarment Certification</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>                             |
|---|-------------------------------------|--------------------------|--------------------------|--|
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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...”</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |
| <b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>                             |
| <p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>   | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |
| <b>Controlled Substance/Product with Abuse Potential</b>  | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>                             |
| <p><u>For NMEs:</u><br/>Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u><br/><i>Date of consult sent to Controlled Substance Staff:</i><br/><b>December 30, 2014</b></p>   | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |  |
| <b>Pediatrics</b>   | <b>YES</b>                          | <b>NO</b>                | <b>NA</b>                | <b>Comment</b>                             |
| <p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration</i></p>   | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                          | PeRC meeting scheduled for August 19, 2015 |

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 12/09/2014

7

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|--|---|-------------------------------------|-------------------------------------|---|
| <i>trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> |   |                                     |                                     |   |
| <b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>   | <input checked="" type="checkbox"/>   | <input type="checkbox"/>            | <input type="checkbox"/>            |   |
| <i>If no, may be an RTF issue - contact DPMH for advice.</i>   |   |                                     |                                     |   |
| <b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>  | <input type="checkbox"/>  | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |   |
| <i>If no, may be an RTF issue - contact DPMH for advice.</i>   |   |                                     |                                     |   |
| <b><u>BPCA:</u></b>  |   |                                     |                                     |   |
| Is this submission a complete response to a pediatric Written Request?   | <input type="checkbox"/>  | <input checked="" type="checkbox"/> |                                     |   |
| <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>  |   |                                     |                                     |   |
| <b>Proprietary Name</b>  | <b>YES</b>  | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>  |
| Is a proposed proprietary name submitted?  | <input checked="" type="checkbox"/>   | <input type="checkbox"/>            | <input type="checkbox"/>            |   |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>   |   |                                     |                                     |   |
| <b>REMS</b>  | <b>YES</b>  | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>  |
| Is a REMS submitted?   | <input checked="" type="checkbox"/>   | <input type="checkbox"/>            | <input type="checkbox"/>            | This product will be part of the class ERLA REMS. Consult sent. |
| <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>   |   |                                     |                                     |   |
| <b>Prescription Labeling</b>   | <input type="checkbox"/> <b>Not applicable</b>  |                                     |                                     |   |
| Check all types of labeling submitted.   | <input checked="" type="checkbox"/> Package Insert (PI)<br><input type="checkbox"/> Patient Package Insert (PPI)<br><input checked="" type="checkbox"/> Instructions for Use (IFU)<br><input checked="" type="checkbox"/> Medication Guide (MedGuide)<br><input type="checkbox"/> Carton labels<br><input checked="" type="checkbox"/> Immediate container labels<br><input type="checkbox"/> Diluent<br><input type="checkbox"/> Other (specify) |                                     |                                     |   |
|  | <b>YES</b>  | <b>NO</b>                           | <b>NA</b>                           | <b>Comment</b>  |
| Is Electronic Content of Labeling (COL) submitted in SPL format?   | <input checked="" type="checkbox"/>   | <input type="checkbox"/>            |                                     |   |
| <i>If no, request applicant to submit SPL before the filing date.</i>  |   |                                     |                                     |   |

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/09/2014

8

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|--|--|--------------------------|-------------------------------------|--|
| Is the PI submitted in PLR format? <sup>4</sup>  | <input checked="" type="checkbox"/>  | <input type="checkbox"/> |                                     |  |
| <b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?<br><br><i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/>   | <input type="checkbox"/> | <input checked="" type="checkbox"/> |  |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?  | <input checked="" type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>            | Consult sent to OPDP.                      |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)  | <input checked="" type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>            | Consult sent to PLT.                       |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?   | <input checked="" type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>            | Consult sent to DMEPA.                     |
| <b>OTC Labeling</b>  | <input checked="" type="checkbox"/> <b>Not Applicable</b>  |                          |                                     |  |
| Check all types of labeling submitted.   | <input type="checkbox"/> Outer carton label<br><input type="checkbox"/> Immediate container label<br><input type="checkbox"/> Blister card<br><input type="checkbox"/> Blister backing label<br><input type="checkbox"/> Consumer Information Leaflet (CIL)<br><input type="checkbox"/> Physician sample<br><input type="checkbox"/> Consumer sample<br><input type="checkbox"/> Other (specify) |                          |                                     |  |
|  | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>                             |
| Is electronic content of labeling (COL) submitted?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>   | <input type="checkbox"/> |                                     |  |
| Are annotated specifications submitted for all stock keeping units (SKUs)?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |  |
| If representative labeling is submitted, are all represented SKUs defined?<br><br><i>If no, request in 74-day letter.</i>  | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |  |
| All labeling/packaging sent to OSE/DMEPA?  | <input type="checkbox"/>   | <input type="checkbox"/> | <input type="checkbox"/>            |  |
| <b>Other Consults</b>  | <b>YES</b>   | <b>NO</b>                | <b>NA</b>                           | <b>Comment</b>                             |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)   | <input checked="" type="checkbox"/>  | <input type="checkbox"/> | <input type="checkbox"/>            | Consult sent to MHT for PLLR label review. |

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

| <b>Meeting Minutes/SPAs</b>  | <b>YES</b>                          | <b>NO</b>                           | <b>NA</b> | <b>Comment</b>  |
|--|-------------------------------------|-------------------------------------|-----------|---|
| End-of Phase 2 meeting(s)?<br><b>Date(s):</b> November 19, 2010<br><br><i>If yes, distribute minutes before filing meeting</i>   | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |           |   |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?<br><b>Date(s):</b> April 11, 2014<br><br><i>If yes, distribute minutes before filing meeting</i>  | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |           |   |
| Any Special Protocol Assessments (SPAs)?<br><b>Date(s):</b> July 21, 2011 and December 2, 2011<br><br><i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |           | A SPA was submitted and comments sent, but there was no agreement based on Statistical missing data methodology uncertainty |

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** January 29, 2015

**BACKGROUND:** ALO-02/Troxyca ER, is a combination opioid analgesic (oxycodone) + sequestered opioid antagonist (naltrexone). This will be a 505(b)(2) application referencing Roxicodone and Revia. The Sponsor requested Priority review based on their proposed abuse-deterrent (AD) formulation, however it will not be granted as the Sponsor did not conduct head-to-head studies with Oxycontin, a previously approved AD formulation.

**REVIEW TEAM:**

| Discipline/Organization             | Names                      |                      | Present at filing meeting? (Y or N) |
|-------------------------------------|----------------------------|----------------------|-------------------------------------|
| Regulatory Project Management       | RPM:                       | Diana Walker         | Y                                   |
|                                     | CPMS/TL:                   | Parinda Jani         | N                                   |
| Cross-Discipline Team Leader (CDTL) | Joshua Lloyd               |                      | Y                                   |
| Division Director/Deputy            | Sharon Hertz               |                      | Y                                   |
| Office Director/Deputy              | Curt Rosebraugh/Mary Parks |                      | N                                   |
| Clinical                            | Reviewer:                  | Elizabeth Kilgore    | Y                                   |
|                                     | TL:                        | Joshua Lloyd         | Y                                   |
| Clinical Pharmacology               | Reviewer:                  | Suresh Naraharisetti | Y                                   |
|                                     | TL:                        | Yun Xu               | Y                                   |
| Biostatistics                       | Reviewer:                  | Feng Li              | Y                                   |
|                                     | TL:                        | Freda Cooner         | Y                                   |

|   |           |                            |   |
|---|-----------|----------------------------|---|
| Nonclinical<br>(Pharmacology/Toxicology)                  | Reviewer: | Elizabeth Bolan            | Y |
|   | TL:       | Daniel Mellon              | Y |
| OPQ Process and Facilities                                | Reviewer: | Yong Hu                    | Y |
|   | TL:       | Zhigang Sun                | N |
| OPQ (CMC)   | Reviewer: | DS: Ben Stevens<br>DP: tbd | N |
|   | TL:       | Ciby Abraham               | Y |
| Biopharmaceutics  | Reviewer: | Albert Chen                | Y |
|   | TL:       | John Duan                  | N |
| Facility Review/Inspection                                | Reviewer: | tbd                        | N |
|   | TL:       | tbd                        | N |
| OSE/DMEPA (proprietary name,<br>carton/container labels)) | Reviewer: | James Schlick              | Y |
|   | TL:       | Vicky Borders-Hemphill     | Y |
| OSE/DRISK (REMS)  | Reviewer: | Danny Gonzalez             | Y |
|   | TL:       | Kim Lehrfeld               | Y |
| MHT   | Reviewer: | Miriam Dinatale            | Y |
|   | TL:       | Tamara Johnson             | Y |

|                                  |             |   |   |
|----------------------------------|-------------|---|---|
| Bioresearch Monitoring (OSI)     | Reviewer:   | John Lee                                    | Y |
|                                  | TL:         | Janice Pohlman                              | N |
| Controlled Substance Staff (CSS) | Reviewer:   | Studies: James Tolliver<br>Stats: Ling Chen | Y |
|                                  | TL:         | Silvia Calderon                             | Y |
| PLT                              | Reviewer:   | Morgan Walker                               | N |
|                                  | TL:         | Barbara Fuller                              | N |
| OPDP                             | Jessica Fox |   | N |

**FILING MEETING DISCUSSION:**

|  |   |
|--|---|
| <p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <input type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO<br><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO<br><br>PK studies |
| <ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> No comments  |
| <p><b>CLINICAL</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input type="checkbox"/> Review issues for 74-day letter              |
| <ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>  | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO  |

|   |  |
|---|--|
|   |  |
| <ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>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</i></li> </ul> | <input type="checkbox"/> YES<br>Date if known:<br><input type="checkbox"/> NO<br><input checked="" type="checkbox"/> To be determined<br><br>Reason:   |
| <ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>   | <input checked="" type="checkbox"/> Not Applicable<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b> Will work with clinical to determine HAL study sites to inspect.</p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO   |
| <p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><br><input type="checkbox"/> Review issues for 74-day letter |
| <p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE   |

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|--|---|
| <p><b>Comments:</b> Impurity specification.</p>  | <input checked="" type="checkbox"/> Review issues for 74-day letter   |
| <p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Questions concerning the impurities and qualification.</p>   | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> FILE<br><input type="checkbox"/> REFUSE TO FILE<br><input checked="" type="checkbox"/> Review issues for 74-day letter |
| <p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>  | <input type="checkbox"/> YES<br><input checked="" type="checkbox"/> NO  |
| <p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>   | <input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO  |
| <p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> This will be done following the new OPQ process.</p>  | <input type="checkbox"/> Not Applicable<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input checked="" type="checkbox"/> YES<br><input type="checkbox"/> NO           |
| <p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>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?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul> | <input checked="" type="checkbox"/> N/A<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO<br><input type="checkbox"/> YES<br><input type="checkbox"/> NO                                 |

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|---|---|
|   |   |
| <ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>   |   |
| <ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul> | <input type="checkbox"/> YES<br><input type="checkbox"/> NO |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>  | <input type="checkbox"/> YES<br><input type="checkbox"/> NO |
| <ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>                                    | <input type="checkbox"/> YES<br><input type="checkbox"/> NO |

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Sharon Hertz, MD, Acting Director, DAAAP

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): N/A

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

Mid-Cycle: May 19, 2015

PeRC Meeting: August 19, 2015

Wrap-up: September 9, 2015

Reviews due: September 14, 2015

Labeling due to Sponsor: September 21, 2015

CDTL memo due: September 28, 2015

**Comments:** Team meetings and labeling meeting dates not listed.

| <b>REGULATORY CONCLUSIONS/DEFICIENCIES</b> |  |
|--|--|
| <input type="checkbox"/>                   | The application is unsuitable for filing. Explain why:   |
| <input checked="" type="checkbox"/>        | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |
| <b>ACTIONS ITEMS</b>                       |  |
| <input checked="" type="checkbox"/>        | 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).  |
| <input type="checkbox"/>                   | If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).  |
| <input type="checkbox"/>                   | 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.  |
| <input type="checkbox"/>                   | 351(k) BLA/supplement: If filed, send filing notification letter on day 60   |
| <input type="checkbox"/>                   | <p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>   |
| <input checked="" type="checkbox"/>        | Send review issues/no review issues by day 74  |
| <input checked="" type="checkbox"/>        | Conduct a PLR format labeling review and include labeling issues in the 74-day letter  |
| <input type="checkbox"/>                   | Update the PDUFA V DARRTS page (for applications in the Program)   |
| <input type="checkbox"/>                   | Other  |

Annual review of template by OND ADRA's completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANA L WALKER  
02/11/2015

PARINDA JANI  
02/11/2015