CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208090Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208090
Applicant Name	Collegium Pharmaceuticals, Inc.
Date of Submission	February 26, 2016
PDUFA Goal Date	April 26, 2016
Proprietary Name / Established (USAN) Name	Xtampza ER/ Oxycodone Extended-Release Capsules
Dosage Forms / Strength	Capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg of oxycodone base, equivalent 10, 15, 20, 30, and 40 mg oxycodone hydrochloride
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.
Action:	Approval

Material Reviewed/Consulted: OND Action Package, including:	
Pharmacology Toxicology Review	Grace S. Lee, PhD, DABT, R. Daniel Mellon, PhD, Timothy McGovern, PhD
Office of Pharmaceutical Quality: CMC /OBP /Microbiology Review	Xiaobin Shen, PhD, Tarun Mehta, PhD, Fang Wu, PhD, John Duan, PhD, Steven Kinsley, PhD, Christina Capacci-Daniel, Derek Smith, Ciby Abraham, PhD, Julia Pinto, PhD
OSI	John Lee MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
OSE/DMEPA	James Schlick, RPh, MBA, Vicky Borders-Hemphill, PharmD, Irene Z. Chan, PharmD, BCPS, Todd Bridges, RPh
OSE/DRISK	Danny S. Gonzalez, Pharm D, MS, Joan Blair, RN, MPH, Kim Lehrfeld, PharmD, Cynthia LaCivita, PharmD
OPDP/DCDP	Koung Lee, RPh, MS, Jessica Fox
OMP/DMPP	Morgan Walker, PharmD, MBA, Barbara Fuller, PharmD

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs
ORP =Office of Regulatory Policy
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
DPMH =Division of Pediatric and Maternal Health

Signatory Authority Review

1. Introduction

Collegium Pharmaceutical, Inc. has resubmitted this 505(b)(2) new drug application for Xtampza ER (oxycodone extended-release capsules), an extended-release formulation of oxycodone with properties intended to deter abuse by the oral, intranasal and intravenous routes of administration. The Applicant intends to rely on the Agency's prior findings of efficacy and safety for OxyContin (oxycodone hydrochloride extended release tablets, NDA 022272). The proposed indication is the same as the indication for OxyContin.

2. Background

As described in the Summary Review for Regulatory Action from the first cycle (see Appendix 1), in the initial NDA, the Applicant had provided adequate evidence of efficacy and safety to support approval for the proposed indication, along with evidence to support that Xtampza ER has properties likely to deter abuse by the intranasal and intravenous routes of administration. What was particularly notable from the data submitted in the original NDA is that this formulation was shown to be resistant to dose dumping when chewed or crushed, and it was safe to sprinkle the contents of the capsule on soft food for dosing in patients with dysphagia. The lack of dose dumping in the setting of chewing or crushing is a finding that is a potential safety advantage that benefits the intended patient population for Xtampza ER over other, currently approved extended-release oxycodone products. These properties are the result of the novel formulation (b) (4)
Limited nonclinical data for these excipients, however, resulted in the recommendation to limit the maximum daily dose of Xtampza ER to the equivalent of 320 mg of oxycodone hydrochloride per day. This amount is likely to be more than the total daily dose needed by the majority of patients who use opioid analgesics on a chronic basis.

As noted in the first Summary Review, the food effect resulting in potential fluctuation in the exposure to oxycodone raised concern within the Division, but following discussion of the data at a joint meeting of the Anesthesia and Analgesia Drug Product Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on September 11, 2015, the committee to voted 23-0 in favor of approving this product. The committee members were reassured by the safety data from the adequate and well-controlled efficacy study conducted by the Applicant, noting that, while patients did not take Xtampza ER consistently with regard to food as directed, there were no signs that this lack of consistency created any safety problems.

As a 505(b)(2) application referencing another extended-release oxycodone product with the same proposed indication, the Applicant was informed that no additional nonclinical studies of oxycodone would be required to support the safety of oxycodone. However, it was noted that there were novel excipients and a number of postmarketing requirements were outlined that are still applicable to evaluate the safety of these excipients at total daily doses of greater than 320 mg oxycodone per day.

There were a number of concerns raised (b) (4) Based on results from an inspection and the results of a trial manufacture of one commercial scale batch, the OPQ team concluded that additional development work was needed to support the commercial scale manufacturing process. As a result, the recommendation for approval would have limited the Applicant to the manufacturing process used for the (b) (4) kg pilot scale batch. Information (b) (4) of (b) (4) kg was submitted and reviewed in conjunction with this resubmission of the application.

3. CMC/Device

The drug product consists of a capsule filled with microspheres made up of a wax-based solid solution of oxycodone drug in a hydrophobic matrix. The microspheres (b) (4) provide the abuse-deterrent characteristics of the formulation. (b) (4)

The OPQ team reviewed the Applicant's proposal to address the deficiencies (b) (4) submitted as an amendment to NDA 208090 on February 17, 2016.

Drug Product Review

Dr. Shen evaluated the Applicant's proposal (b) (4) The following is from the OPQ review:

> The Comparability Protocol was submitted (b) (4) The protocol was evaluated in the first drug product review completed on 08-Sep-2015 and deemed acceptable, from the DP stand point.

(b) (4)

Dr. Shen concluded the following:

> The request (b) (4) is granted from CMC perspective. (b) (4)

Process Assessment

Dr. Mehta reviewed the response to the (b) (4) deficiencies and concluded:

> Considering all this information, we recommend (b) (4) The data for validation batches should be submitted to the Agency in a Special Report.

Biopharmaceutics

From Dr. Wu's review:

> ONDP-Biopharmaceutics has reviewed the amendment to NDA 208090 submitted on February 17, 2016. The provided data support the acceptability of the (b) (4) kg commercial batch for (b) (4) Xtampza ER™ Capsules (Oxycodone extended-release capsules (b) (4) after the internal discussion within biopharmaceutics review team and with the CMC review team, no further dissolution profiles comparisons data are requested (b) (4) prior to the approval.
>
> Therefore, from the biopharmaceutics perspective, commercial products at (b) (4) kg scale for 9, 13.5, 18, 27 and 36 mg strength oxycodone extended-release capsules are recommended for APPROVAL.

The overall OPQ conclusions from the combined OPQ review of the resubmission support approval of the product at the commercial batch size. The following is from the OPQ review:

> Based on our internal discussion and the discussion with CMC product reviewer and process reviewer, (b) (4) kg batch size for 9, 13.5, 18, 27 mg and 36 mg strength (all the strengths) is recommended for APPROVAL based on the current submitted data. The reasons are summarized below:
>
> - Dissolution profiles between (b) (4) kg (biobatch) and (b) (4) kg scale batches for (b) (4) oxycodone extended-release capsules are similar in three tested media (pH (b) (4), 4.5 and (b) (4)) (f2>50).
> - For (b) (4) kg batch size, the dissolution profiles (b) (4) are similar in all tested media (pH (b) (4), 4.5 and (b) (4)).
> - The particle size of microspheres is controlled within reasonable limits during the manufacturing process for (b) (4) kg scale.
> - (b) (4)
> - The Applicant commits to submit (b) (4) in a special report in the responses dated 04/14/2016, which is in response to the information request (IR) by the Agency dated 04/12/2016.

I concur with the conclusions reached by the Office of Pharmaceutical Quality review team regarding the acceptability of approving Xtampza ER, including accepting the special report for the data from process validation batches for the five strengths. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this resubmission. The post marketing requirements identified during the prior review cycle are still applicable.

I continue to concur with the conclusions reached by the pharmacology/toxicology reviewer and for the most part with Drs. Mellon and McGovern. As noted during the prior review cycle, I do not agree that the chronic toxicology studies alone are sufficient as postmarketing requirements, but rather, that the additional studies suggested by Dr. Mellon should be obtained. Exposure to the quantity of wax that would occur with the upper limit of dosing

represents a novel situation and the Applicant was asked to conduct the appropriate studies to provide safety qualification from an early stage in development. In order to label the product for more than 320 mg per day, the reproductive toxicology studies should be conducted in addition to the chronic toxicology studies for the reasons discussed by Dr. Mellon. There are no outstanding pharm/tox issues that preclude approval of Xtampza ER with dosing up to 320 mg per day. Note that the Xtampza ER total daily dose is actually 288 mg because it contains the free base. The 320 mg dose refers to the hydrochloride salt of oxycodone.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted with this resubmission. As noted during the first review cycle, Xtampza ER has a lower oxycodone Cmax and AUC than OxyContin in the fasted state, and comparable AUC with lower Cmax for oxycodone in the fed state. The data are available in the original summary review in Appendix 1. The product will be labeled to be taken with food, with the following language in the Dosage and Administration section of the package insert:

> XTAMPZA ER is administered, twice daily, every 12 hours, and **must be taken with food.** Instruct patients to take XTAMPZA ER capsules with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved. *[see Clinical Pharmacology (12.3)]*.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

No new clinical data were submitted in support of this application. See the discussion of the efficacy data supporting this application in the first summary memo appended below.

8. Safety

No new clinical data were submitted in support of this application. See the discussion of the safety data supporting this application in the first summary memo appended below.

9. Advisory Committee

A second advisory committee was not convened for this submission. See the discussion of the advisory committee held Sept 11, 2015, in the first summary memo appended below.

10. Pediatrics

We concur with the Applicant's request for a waiver for the pediatric studies requirement for ages birth to less than 2 years because studies are impossible or highly impracticable. This is because the number of pediatric patients with chronic pain in this age group is extremely small.

We are deferring submission of required pediatric studies for ages 2-7 years and 7-17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. The required pediatric postmarketing studies are described below.

11. Other Relevant Regulatory Issues

REMS

As previously noted, Xtampza ER will be part of the Extended-release and Long-acting Opioid Analgesic REMS and will be subject to the existing postmarketing required studies to evaluate the risks of abuse, misuse, overdose and death, as well as for follow-up of the effects of the abuse-deterrent properties.

The ER/LA opioid analgesics REMS was approved with the following elements:

- Medication Guide
- Elements to Assure Safe Use
    - Prescriber Training
        - FDA Blueprint for Prescriber Education for Extended-Release and
        - Long-Acting Opioid Analgesics (FDA Blueprint)
        - Patient Counseling Document (PCD) on Extended-Release and Long-Acting Opioid Analgesics
        - Letters to DEA-Registered Prescribers
        - Letters to Professional Organizations/Licensing Boards
        - REMS website
- Timetable for Submission of Assessments

Patent Certification

The Applicant has provided Paragraph IV certifications as to each patent listed in the Orange Book for OxyContin. The prior patent infringement suit initiated by Purdue Pharma, holder of the OxyContin NDA, regarding US Patent Nos 7,674,799; 7,674,800; and 7,683072 had

been dismissed by the District of Delaware, and on February 9, 2016, was dismissed by the Massachusetts District Court. The Applicant notes that the court's dismissal terminated the statutory 30-month stay on the approval of Xtampza ER. The Applicant notes that 3-year exclusivity coded M-153 for OxyContin expires on April 16, 2016, and although the Applicant had also previously asserted that the M-153 exclusivity was narrow and could not serve as a basis to delay approval Xtampza ER, the period of exclusivity has ended and the question of whether the scope of exclusivity was narrow or not is now moot.

Abuse Deterrence

The studies evaluating the abuse-deterrent properties of Xtampza ER are described in the first cycle summary memo appended below. In vitro studies support a finding that Xtampza ER has physicochemical properties that can be expected to deter intravenous abuse. In vitro data and the results of clinical abuse potential studies support a conclusion that Xtampza ER can be expected to deter intranasal abuse. The clinical abuse potential study that evaluated the abuse-deterrent properties of Xtampza ER for abuse by the oral route after chewing or crushing did not support a finding that Xtampza ER can be expected to deter oral abuse as there was no significant difference in the results of the outcome measure "take drug again". However, the pharmacokinetic data following oral administration of crushed or chewed Xtampza ER revealed that there was no increase in release of oxycodone compared to the intact state. This information is important with regard to patient safety, but alone cannot support a finding that Xtampza ER is likely to deter oral abuse. This will be conveyed in the labeling. To support such a finding, the Applicant must conduct an adequate and well-controlled oral human abuse potential study.

12. Labeling

Labeling reviews of the package insert were conducted by the Division of Medication Error Prevention and Analysis in the Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology. The suggested changes were incorporated into the labeling. The proprietary name, Xtampza ER, was found acceptable.

The product labeling will include information about the results of the evaluation of abuse-deterrent properties of Xtampza, as described in the guidance[1], "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." To provide an accurate characterization of the data from the evaluation of abuse-deterrent properties, results from the in vitro and in vivo studies will be included. Overall there is evidence that Xtampza can be expected to deter abuse by the intravenous route as characterized by results from the in vitro evaluation of syringeability, and by the intranasal route as characterized by the results of in vitro, pharmacokinetic, and abuse potential studies. The oral clinical abuse potential study did not show a difference in the "take drug again" endpoint, and as such, could be excluded from the label. However, the

[1] Abuse-Deterrent Opioids — Evaluation and Labeling, Guidance for Industry, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf

pharmacokinetic evaluation of oral ingestion of crushed and chewed Xtampza demonstrated a lack of dose dumping. In isolation, this information might be over-interpreted to reflect an oral abuse-deterrent effect, and for that reason, the oral clinical abuse potential study which failed to support a conclusion of potential oral abuse-deterrent effects will be included in the labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval

- Risk Benefit Assessment

The Applicant has provided adequate evidence of efficacy and safety to support approval for the proposed indication, even with the demonstrated effect of food on the bioavailability of oxycodone from Xtampza ER. In addition, the Applicant has provided adequate evidence to support that Xtampza ER has properties likely to deter abuse by the intranasal and intravenous routes of administration. However, what stands out about this product is that the formulation is resistant to dose dumping when chewed or crushed, and can be sprinkled on soft food for dosing in patients with dysphagia This results in a safety advantage for Xtampza ER over other, currently approved extended-release oxycodone products that benefits the intended patient population. These properties are the result of the novel formulation. The (b) (4) lack of adequate nonclinical coverage for these excipients results in the need to limit the maximum daily dose of Xtampza ER to the equivalent of 320 mg of oxycodone hydrochloride per day. This amount is likely to be more than the total daily dose needed by the majority of patients who use opioid analgesics on a chronic basis. However, because some patients do require more than this, sponsors are generally required to provide adequate safety qualification as a condition of approval. Because Xtampza ER has abuse-deterrent properties, and especially because Xtampza ER has the ability to resist dose dumping when taken orally after chewing or crushing, and can be sprinkled on food for patients with dysphagia, there are possible safety advantages for patients not available in other oxycodone extended-release formulations.

The Applicant has adequately addressed issues (b) (4) and has agreed to submit (b) (4) in a special report.

There are no outstanding patents or exclusivity that preclude approval of this product at this time.

- Recommendation for Postmarketing Risk Management Activities

Xtampza ER will be part of the Extended-release and Long-acting Opioid Analgesic REMS.

- Recommendation for other Postmarketing Study Commitments

The following section describes the required postmarketing studies that will be required for this NDA, presented in the language from the action memo.

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

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

- Assess the known serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of extended-release and long-acting (ER/LA) opioid analgesics, of which XTAMPZA ER (oxycodone) extended-release capsules is a member;
- Assess the known serious risks of misuse and abuse by determining whether the properties intended to deter misuse and abuse of XTAMPZA ER (oxycodone) extended-release capsules actually result in a meaningful decrease in misuse and abuse, and their consequences of addiction, overdose, and death, in the community;
- Identify an unexpected risk of serious systemic histopathological changes, teratogenicity, serious embryo-fetal developmental, and/or post-natal developmental adverse events, or cancer due to chronic exposure to the excipients myristic acid, beeswax, and carnauba wax in XTAMPZA ER (oxycodone) extended-release capsules or contaminants in the beeswax used to manufacture the drug product.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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 must address at a minimum the following specific objectives:

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.

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

Final Protocol Submission:	11/2015
Interim Report (Cumulative Enrollment of 470 patients)	05/2017
Interim Report (Cumulative Enrollment of 1,042 patients)	09/2017
Interim Report (Cumulative Enrollment of 1,609 patients)	01/2018
Interim Report (Cumulative Enrollment of 2,300 patients)	06/2018
Study Completion:	10/2019
Final Report Submission:	03/2020

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.

This study must address at a minimum the following specific objectives:

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.

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

Final Protocol Submission:	11/2014
Study Completion:	04/2019
Final Report Submission:	09/2019

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Final Protocol Submission:	03/2015
Study Completion:	09/2018
Final Report Submission:	12/2018

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

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

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

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies to provide the best information possible. The milestones noted above reflect those that were specified at the time the study requirements were issued for the class of ER/LA opioid analgesics.

Additionally, FDA has determined that you are also required to conduct the following individual postmarketing studies of XTAMPZA ER (oxycodone) extended-release capsules:

2966-3 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2966-4, conduct a descriptive study that analyzes data on the following:

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

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

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

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

This study will be conducted according to the following schedule:

Draft Protocol Submission	08/2016
Final Protocol Submission:	12/2016
Study Completion:	12/2017
Final Report Submission:	06/2018

2966-4 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of XTAMPZA ER (oxycodone) extended release capsules actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of XTAMPZA ER (oxycodone) extended release capsules and should incorporate recommendations contained in Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry (April 2015). Assessing the

impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

This study will be conducted according to the following schedule:

Draft Protocol Submission	08/2018
Final Protocol Submission:	12/2018
Study Completion:	12/2020
Final Report Submission:	06/2021

Study protocols, proposed statistical analysis plans (SAPs), and the milestones for each study conducted under PMR 2966-4 must be mutually agreed upon with FDA, and informed by results from PMR 2966-3. Protocols and SAPs should be submitted to FDA prior to initiating these formal studies, in sufficient time for the Agency to review and provide comments, and concur with the protocols. The protocols and SAPs should incorporate formal hypothesis testing in addition to descriptive analyses and should include power calculations based on actual data.

2966-5 Conduct a chronic (6-month) repeat-dose general toxicology study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2017
Study Completion:	07/2018
Final Report Submission:	01/2019

2966-6 Conduct a chronic (9-month) repeat-dose general toxicology study in the dog model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2017
Study Completion:	02/2018
Final Report Submission:	09/2018

2966-7 Conduct a fertility and early embryonic development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2017
Study Completion:	04/2018
Final Report Submission:	10/2018

2966-8 Conduct an embryo-fetal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2017
Study Completion:	01/2018
Final Report Submission:	07/2018

2966-9 Conduct an embryo-fetal development study in the rabbit model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2017
Study Completion:	06/2018
Final Report Submission:	12/2018

2966-10 Conduct a pre- and post-natal development study in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2018
Study Completion:	03/2019
Final Report Submission:	11/2019

2966-11 Conduct a carcinogenicity assessment in the rat model testing a mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2018
Study Completion: 03/2021
Final Report Submission: 03/2022

2966-12 Conduct a carcinogenicity assessment in the mouse model testing the mixture of beeswax, carnauba wax, and myristic acid that is representative of the drug product composition.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2018
Study Completion: 04/2021
Final Report Submission: 04/2022

2966-13 Complete a detailed analysis of the beeswax employed in your drug product for potential residual levels of environmental and apicultural sources of contaminants, based on a thorough review of the apicultural practices across the globe and known contaminants in wax. Provide full validated analytical methods used for testing of the contaminants, including the level of detection. Provide a justification of the safety levels of contaminants present and the need for routine testing of the beeswax prior to use in the manufacture of the drug product.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2016
Study Completion: 07/2017
Final Report Submission: 09/2017

2966-14 Conduct a study to characterize the levels of (b) (4) in the final drug product formulation and propose a release specification to adequately control (b) (4) in the drug product.

The timetable you submitted on March 3, 2016, states that you will conduct this study according to the following schedule:

Study Completion: 12/2016
Final Report Submission: 02/2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which XTAMPZA ER (oxycodone) extended-release capsules is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

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

Final Protocol Submission:	11/2014
Trial Completion:	02/2019
Final Report Submission:	08/2019

34 Pages have been Withheld in Full as duplicate copy of MedR 11.6.15 Summary Review for Regulatory Action immediately following this page

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/s/

SHARON H HERTZ
04/26/2016