CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209777Orig1s000

Trade Name:	ROXYBOND tablets, 5 mg, 15 mg, and 30 mg.
Generic Name:	Oxycodone Hydrochloride
Sponsor:	Inspirion Delivery Sciences, LLC
Approval Date:	4/20/2017
Indication:	For the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

CENTER FOR DRUG EVALUATION AND RESEARCH

209777Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

209777Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209777

NDA APPROVAL

Inspirion Delivery Sciences, LLC
c/o Cardinal Health Regulatory Sciences
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Attention: Debra Aub Webster, PhD
Principal Scientist, Regulatory Affairs and Product Development

Dear Dr. Webster:

Please refer to your New Drug Application (NDA) dated and received October 21, 2016, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ROXYBOND (oxycodone hydrochloride) tablets, 5 mg, 15 mg, and 30 mg.

This new drug application provides for the use of ROXYBOND for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the attached carton and immediate container labels, submitted on March 30, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209777**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

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

- Assess the known serious risks of misuse and abuse by determining whether the properties intended to deter misuse and abuse of ROXYBOND actually result in a meaningful decrease in misuse and abuse, and their related clinical outcomes, addiction, overdose, and death, in the community.

- Identify an unexpected risk of serious adverse outcome of cancer due to chronic exposure to the excipient (b) (4) in ROXYBOND.

- Identify an unexpected risk of serious adverse outcomes such as focal myocarditis and hepatotoxicity due to chronic exposure to the excipient (b) (4) in ROXYBOND.

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 studies:

3204-1 Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4)

The timetable you submitted on April 13, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2018
Study Completion:	07/2019
Final Report Submission:	12/2019

3204-2 Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4)

The timetable you submitted on April 13, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2017
Study Completion:	05/2018
Final Report Submission:	10/2019

3204-3 Conduct a 2-year rodent oral carcinogenicity assessment of (b) (4)

The timetable you submitted on April 13, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2018
Study Completion:	04/2021
Final Report Submission:	09/2021

3204-4 In order to provide meaningful baseline data to support the hypothesis-testing studies which will be required under a separate PMR in the future, conduct a descriptive study that analyzes data on the following:

1) Utilization of ROXYBOND and selected comparators: Reports should include nationally-projected quarterly dispensing data, overall and by age group and census region;

AND

2) Abuse of ROXYBOND and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for ROXYBOND 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:	12/2017
Draft Statistical Analysis Plan Submission:	12/2017
Final Protocol Submission:	06/2018
Final Statistical Analysis Plan Submission:	06/2018
Interim Report #1:	03/2019
Interim Report #2:	03/2020
Study Completion:	03/2021
Final Report Submission:	06/2021

Following satisfactory fulfillment of the listed above, you will be expected to conduct the following study:

Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of ROXYBOND 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 ROXYBOND 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*.

Because the formal observational studies are dependent on data collected in PMR 3204-4, we are not attaching milestone dates for those studies *at this time*. At an appropriate time in the future, the language for these studies, the PMR set number, and the milestone dates will be formalized in a letter from FDA.

Submit the protocols to your IND 105951, with a cross-reference letter to this NDA. Submit and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

We remind you of your postmarketing commitments:

3204-5 As part of the ongoing stability studies, commit to repeating the small volume extraction studies, using water and solvents at pH 2 and 3.5, using tablets that are pre-treated with heat and no heat, crushed and intact. Further use the same study conditions in the completed in vitro studies submitted to the NDA, to demonstrate that there is no change in syringeability of the product and in the extraction recovery of the drug product stored over time. Commit to repeating these studies yearly.

The timetable you submitted on April 18, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2017
Study/Trial Completion:	04/2022
Interim Annual Submission:	04/2018

Interim Annual Report:	04/2019
Interim Annual Report:	04/2020
Interim Annual Report:	04/2021
Final Report Submission:	09/2022

3204-6 Commit to the submission of an updated in-process sampling plan and associated acceptance criteria for the stratified (b) (4) for the (b) (4) coated tablets to ensure that batches of drug products meet appropriate statistical quality criteria. The proposed statistical plan and acceptance criteria shall be adequate to ensure that appropriate quality conclusions can be made about this in-process material based on final critical quality attributes and shall be justified with supporting statistical analyses or rationale.

The timetable you submitted on April 20, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study/Trial Completion:	N/A
Final Report Submission:	N/A
Other:	N/A

Submit clinical protocols to your IND 105951 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

EXPIRATION DATING

ROXYBOND (oxycodone hydrochloride) tablets, 5 mg, 15 mg, and 30 mg, in 100 count high-density polyethylene (HDPE) bottles are granted an expiry dating of 36 months when stored at 25°C (77°F) with excursions permitted to15° to 30°C (59° to 86°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Taiye Ayoola, PharmD, Regulatory Project Manager, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

SHARON H HERTZ
04/20/2017