CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209777Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209777 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: RoxyBond Established/Proper Name: Oxycodone Hydrochloride Dosage Form: Immediate-Release Tablets		Applicant: Inspirion Delivery Sciences, LLC Agent for Applicant (if applicable): Debra Aub Webster, PhD
RPM: Taiye Ayoola		Division: Division of Anesthesia, Analgesia, and Addiction Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

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

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: April 13, 2017

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is April 21, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Opioid analgesic
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval; April 20, 2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Conditionally Acceptable: 1/26/17 Review: 1/13/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 12/15/16 None DMEPA: ☒ 1/16/17, 3/29/17 None DMPP/PLT (DRISK): ☒ 3/30/17 None OPDP: ☒ 3/28/17None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	12/15/16 ☐ Not a (b)(2) 3/22/17
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: RoxyBond is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Inspirion Delivery Sciences is exempt from the requirement for an assessment of the safety and effectiveness of the product for the claimed indication (s) in pediatric patients under the Pediatric Research Equity Act (PREA) (21 USC 355c)	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included Filing Review Issues Identified letter dated 12/15/16, NDA Acknowledgment letter dated 11/1/16, and information requests dated 11/4/16, 11/7/16, 11/8/16, 11/14/16, 12/2/16, 12/8/16, 12/23/16, 12/28/16, 1/19/17, 1/23/17, 1/24/17, 2/2/17, 2/8/17, 2/14/17, 2/23/17, 3/14/17, 3/20/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Pre-IND meeting 11/24/09

❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	4/5/17
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 4/20/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 4/14/17
PMR/PMC Development Templates *(indicate total number)*	☐ None 4 Templates; 6 PMR/PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	4/14/17
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical review: 4/14/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 12/1/16, 3/29/17
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/7/16, 3/22/17, 3/29/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested 2/27/17
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 1/8/14 (for referenced IND 105951), 3/31/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None Biopharm 3/27/17 Drug Substance 3/28/17 Drug Product 3/29/17 Process 3/30/17 Facilities 4/20/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Drug Product Review 3/29/17
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable: 4/20/17 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

TAIYE AYOOLA
04/27/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Information Request
Date: Monday, March 20, 2017 5:32:00 PM
Importance: High

Hello Debra,

Regarding the container label for RoxyBond, we recommend that the following be implemented:

1. Decrease the font size of the CII symbol to ensure that the proprietary name, established name, and strength are the most prominent information on the label.
2. Revise the dispensing statement on the side panel to read: "Dispense in a well-closed container as defined in the USP/NF, with a child-resistant closure."
3. Add updated NDC numbers on the container labels for our evaluation.
4. Place the established name for the drug substance into parenthesis as: (Oxycodone Hydrochloride) tablets.
5. Per USP salt policy, add an active moiety equivalence language to the label for each strength such as: (equivalent to x mg oxycodone).

Additionally, please let us know how soon you can provide the new container label mock-ups for our review.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
03/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209777

INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION

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, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for RoxyBond (Oxycodone ARIR) Immediate-Release Oral Tablets, 5 mg, 15 mg, and 30 mg.

We also refer to your amendments dated:

November 17, 2016
December 15, 2016
January 10, 13, 25, and 31, 2017
February 3 and 16, 2017
March 2, 6, and 9, 2017

This amendment does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendment dated:

November 17, 2016
December 15, 2016
January 10, 13, 25, and 31, 2017
February 3 and 16, 2017
March 2, 6, and 9 2017

If you have any questions, contact me at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

TAIYE AYOOLA
03/14/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Information Request
Date: Thursday, February 23, 2017 1:16:00 PM
Importance: High

Dear Debra,

Please respond to the following information requests by **Wednesday, March 1, 2017.**

1. Submit a revised label based on the most recently approved Roxicodone label.

2. We found your summary of biopharmaceutic studies and associated analytical methods. However, we are not able to locate the bioanalytical reports SAI-1212217 for Study O-ARIR-003, SAI-1403426 and SAI-1407495 for Study O-ARIR-002, and SAI-1408517 for Study O-ARIR-006. Provide the locations for these full reports if you have submitted them to us or submitted them by March 1, 2017 if you have not done so.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

Please ensure that you have a secure email address for receiving confidential information. Contact the Office of Information Management (OIM) to request secure email via SecureEmail@fda.hhs.gov.

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/s/

TAIYE AYOOLA
02/23/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777 IR/Advice
Date: Tuesday, February 14, 2017 3:29:00 PM
Importance: High

Hello Debra,

We note that you described the delay of your responses to our information request dated December 23, 2016, in your February 13, 2017 email as follows: *"It was originally thought that we would have top line results this week and be able to provide a preliminary response by email on February 17. However, it is now apparent that the modeling will not be completed until next week at the earliest, with the final report sometime after that".*

Your proposal for submitting the in silico PBPK absorption modeling and simulation data by next week and the final report sometime after that (by the end of February, 2017) is acceptable. However, if you encounter some issues with your model development and validation, we remind you that, based on the in vitro performance of clinical batches, passing the recommended acceptance criterion of "NLT (b)(4)% at 30 minutes" for all three proposed strengths: 30mg, 15 mg and, 5 mg of Oxycodone ARIR tablets, is highly feasible.

Let us know if this email response does not address your question, and if you would still need a teleconference with the Agency.

Regards,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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/s/

TAIYE AYOOLA
02/14/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777 Information Request
Date: Wednesday, February 08, 2017 11:04:00 AM
Attachments: image001.png
Importance: High

Hello Debra,

This is a follow-up to the January 31, 2017 responses which you provided to our information request dated January 24, 2017. Please respond to the subsequent information request by **12 pm (EST) on Monday, February 13, 2017.**

Original information request dated January 24, 2017:

1. **Table 1 on page 15 of the label, provide details on how you calculated the "Crushed Intranasal ROXICODONE vs. Crushed Intranasal RoxyBond Percent Reduction".**

Sponsor's response dated January 31, 2017:

Table 14.2.1-7 in the clinical study report (CSR) for Study O-ARIR-002 supports the percent reduction in crushed intranasal Roxicodone versus crushed intranasal RoxyBond, which is shown in Table 1 on page 15 of the prescribing information for RoxyBond.

Reviewer's response and information request:

Based on your equation and the values provided in your table, we still could not reproduce your results.

$$percent\ reduction = 100 \times \frac{control - test}{|control - placebo|}$$

For example, for drug liking: percent reduction = 100% x (82.9 – 71.1)/(82.9-53.4) = 40%, not 46.9%.

Submit additional information to explain why our calculation is different from yours.

Table 1. Summary of Maximum Drug Liking (E_{max}), Early Drug Liking (AUE_{0-1} and AUE_{0-2}), and Take Drug Again (E_{max}), Following Administration of RoxyBond, ROXICODONE®, and Placebo in Recreational Opioid Users (N=29)

VAS		Crushed Intranasal RoxyBond 30 mg	Crushed Intranasal ROXICODONE 30 mg	Placebo	Crushed Intranasal ROXICODONE vs. Crushed Intranasal RoxyBond Percent Reduction	Crushed Intranasal ROXICODONE vs. Crushed Intranasal RoxyBond Difference of LS Means (95% CI)
Drug Liking (E_{max})	Mean (SEM)	71.1 (2.23)	82.9 (2.15)	53.4 (1.18)	46.9%	11.93 (7.16, 16.70) $P < .0001$
	Median (Range)	71 (50 to 100)	82 (50 to -100)	51 (50 to 77)	40.0%	
Early Drug Liking (AUE_{0-1})	Mean (SEM)	6.3 (1.06)	19.4 (1.58)	0.9 (0.71)	72.4%	13.12 (10.11, 16.13) $P < .0001$
	Median (Range)	5.5 (-4.8 to 17.5)	21.0 (0.0 to 31.3)	0.0 (-9.5 to 14.5)	70.4%	

Early Drug Liking (AUE_{0-2})	Mean (SEM)	21.4 (2.86)	43.1 (3.32)	2.5 (1.65)	58.9%	21.96 (15.02, 28.90) $P < .0001$
	Median (Range)	20.9 (-1.5 to 57.5)	44.4 (0.0 to 68)	0.0 (-14.0 to 38)	54.4%	
Take Drug Again (E_{max})	Mean (SEM)	62.2 (4.55)	82.1 (3.05)	41.9 (3.73)		20.0 (9.00, 31.00) $P < .0001$
	Median (Range)	62.0 (3 to 99)	86.0 (37 to 100)	50.0 (0.0 to 78)		

Original information request dated January 24, 2017:

2. **You provided the results of your analysis of TEmax in Table 11.4.2.2-2 on page 78 of the protocol. The Agency's statistical analysis results of TEmax are different from yours. Based on the Agency's results, there is no significant difference. Provide the dataset you used and the related SAS code.**

Sponsor's response dated January 31, 2017:

The dataset that was used is the ADVAS dataset, for this parameter, the PARAMCD='LIKTEMAX'. Sponsor also provided the SAS code on how to conduct the analysis of TEmax.
Because the normality assumption was not met (ie, p value of Shapiro-Wilk test < 0.01), rank transformation was applied to the data.

Reviewer's response and information request:

Rank transformation and mixed model approach was pre-specified in your 2013 protocol (with amendment 3) before the publication of FDA guidance in 2015. So it is acceptable in this case. On the other hand, the results from this approach should be interpreted carefully. The mixed model uses the rankings of VAS scores instead of their values as outcome, so it is the result of testing the differences of mean rankings from two treatment arms, not the mean or median of paired differences (in VAS score values) from two treatments. In addition, your protocol also mentioned Hodges-Lehman estimate for the differences in two paired medians with 95% CI of the median differences. **Please provide SAS code on how you calculated the Median Differences (SEM) using Hodges-Lehman estimates with Confidence Intervals.** The actual size of deterrent effect can also be presented by the descriptive analysis such as mean, median and graphic display of individual and treatment arm profiles.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

TAIYE AYOOLA
02/08/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Information Request
Date: Thursday, February 02, 2017 1:44:00 PM
Importance: High

Dear Debra,

With regards to NDA 209777, can you kindly provide an update as to where the study records for the study/studies conducted at CRI are now located/stored? Please respond to this information request by COB (EST) today, Thursday, February 2, 2017.

Thank you,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
02/02/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209777

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Hydrochloride Tablets 5 mg, 15 mg, and 30 mg.

We acknowledge receipt of your correspondence, dated and received November 1, 2016, requesting a review of your proposed proprietary name, RoxyBond.

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

If any of the proposed product characteristics as stated in your November 1, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wendy Brown, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-9140. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager in the Office of New Drugs at 240-402-8561.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

VIKKI S KINSEY
01/26/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/26/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: CSS Statistical Information Request
Date: Tuesday, January 24, 2017 2:54:00 PM
Importance: High

Dear Debra,

Please respond to the following information requests by **COB (EST) on Tuesday, January, 31, 2017**:

1. *For Table 1 on page 15 of the label, provide details on how you calculated the "Crushed Intranasal ROXICODONE vs. Crushed Intranasal RoxyBond Percent Reduction".*

2. *You provided the results of your analysis of TEmax in Table 11.4.2.2-2 on page 78 of the protocol. The Agency's statistical analysis results of TEmax are different from yours. Based on the Agency's results, there is no significant difference. Provide the dataset you used and the related SAS code.*

3. *For the percent reduction, the Agency does not agree that you set the percent reduction to the largest percentage observed in the study in the case where the control was equal to 50. This value should be set to zero or any negative value. There are 6 out of 29 subjects who had placebo response ≥55 for drug liking VAS. We suggest you use the 'Exploratory Percent Reduction' formulation you mentioned in your proposal and replace Figure 2 of the label with the new results.*

4. *Provide the SAS code for the primary statistical analysis, and include how you check the normal assumption.*

An initial email response by the stated due date will be fine. However, kindly follow-up with an official submission to your NDA 209777.

Regards,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

TAIYE AYOOLA
01/24/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Clinical Pharmacology Information Request
Date: Monday, January 23, 2017 9:32:00 AM
Importance: High

Dear Debra,

Please provide a response to the Clinical Pharmacology information that was requested in the *Filing Review Issues Identified* letter dated December 15, 2016 by **COB (EST) on January 31, 2017**:

Clinical Pharmacology Information Request:

1. *For Study O-ARIR-003, provide a comparison of partial AUCs (point estimate and 90% confidential intervals) at all time points from time 0 to 4h (e.g., AUC0-1 h, AUC0-1.5 h, AUC0-2h, AUC0-3h, and AUC0-4h) between the test and the reference treatments. Provide justification that the delayed Tmax for your product under fasted conditions compared to Roxicodone will not affect the efficacy of your product, particularly with regard to onset of action.*

2. *For your 505(b)(2) application, you must establish a scientific bridge to the listed drug Roxicodone. You propose that the bridge between the 30 mg strength of your product and the 30 mg strength of Roxicodone is established by the bioequivalence (BE) study evaluating these two treatments. In addition, you conducted a dose proportionality study across the 5, 15 and 30 mg strengths of your product. However, you have not conducted a BE study between the 5 and 15 mg strengths of your proposed product and Roxicodone. Provide justification for how the bridge is established between these two strengths of your product and Roxicodone.*

Regards,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
01/23/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777 Information Request
Date: Thursday, January 19, 2017 4:42:00 PM
Importance: High

Dear Debra,

In preparation for the upcoming advisory committee meeting, provide a coding system for all the solvents and conditions used in your Category 1 studies by COB (EST) on **Wednesday, January 25, 2017**. You can present this coding system at the closed session of the meeting and the codes will be used in the open session. By using the same system, your background documents and those prepared by the Agency will be harmonized and lead to easier interpretation by the committees.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
01/19/2017

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: RE: NDA 209777 Biopharmaceutics Information Request
Date: Wednesday, December 28, 2016 2:30:00 PM
Attachments: image001.png
Importance: High

Dear Debra,

We acknowledge that you conducted the dose proportionality study (Study O-ARIR-006) using Oxycodone ARIR tablet strengths 5 mg, 15 mg, and 30 mg to compare pharmacokinetic parameters. The *in vivo* clinical study does support that the slower release rate of the 15 mg strength dissolution profile will not affect bioequivalence. It is noted that, for the 15 mg strength used in Study O-ARIR-006, bio-batch #C006913, measured release was over 80% of the labeled amount of drug at 30 minutes, which could be the recommended dissolution acceptance criterion for this product based on the submitted dissolution data for bio-batches for all the strengths at 30 minutes (5 mg (97.2%), 15 mg (84.7%) and 30 mg (98.5%)). However, the 15 mg registration batch #C007113, only releases 78.9% at 30 minutes, which does not meet the criterion of release over (b) (4)% at 30 minutes.

Therefore, in the IR dated 12/23/2016 we asked for justification to show that the slower release rate of the dissolution profile (i.e. batch #C007113) will not affect bioequivalence. To address this concern, you can propose to tighten~~ed~~ the dissolution acceptance criterion based on the dissolution data for bio-batches to *"NLT (b) (4)% (Q) of the labeled amount of oxycodone hydrochloride dissolved in 30 minutes"* instead of the originally proposed criterion (b) (4) or alternatively, provide further evidence to support another proposed dissolution acceptance criterion. Using a verified PBPK (physiologically-based pharmacokinetics) modeling and simulation (e.g. virtual BE (bioequivalence) study) to show that the slower release rate of a dissolution profile will not affect the bioequivalence to the RLD (ROXICODONE) would be considered supportive evidence.

If you require further clarification, we are open to a teleconference.

Thanks,
Taiye

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Tuesday, December 27, 2016 3:02 PM
To: Ayoola, Taiye
Subject: RE: NDA 209777 Biopharmaceutics Information Request

Dear Taiye,
In response to your request for information in email dated 12/23/2106 3:30 PM we would like clarification regarding the request for "supportive data by using verified PBPK (physiologically-based pharmacokinetics) modeling and simulation (e.g. virtual BE (bioequivalence) study) to show that the slower release rate of a dissolution profile will not affect the bioequivalence to the RLD (ROXICODONE)."
As indicated by DAAAP (PIND meeting minutes dated February 16, 2010), the dose proportionality of

the PK of the Oxycodone ARIR tablet strengths in a clinical study was conducted to support marketing of all tablet strengths. A dose proportionality study (Study O-ARIR-006) was conducted using the 5, 15, and 30 mg strengths of RoxyBond in which the pharmacokinetic parameters were compared and found to be dose proportional. We believe this supports that the slower release rate of the dissolution profile will not affect bioequivalence.

Would it be possible to obtain further clarification from the biopharmaceutics reviewer regarding this request for information either by email or informal teleconference?

Thank you for your help.

Regards,
Debra

CardinalHealth
Essential to care™
Logistics
Product
Business
Patient

Debra Aub Webster, PhD
Principal Scientist, Regulatory Affairs and Product Development
Cardinal Health Regulatory Sciences
7400 W 110th St, Suite 300,
Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax |
(b) (6) mobile
debra.webster@Cardinalhealth.com
www.cardinalhealth.com/regulatorysciences

From: Ayoola, Taiye [mailto:Taiye.Ayoola@fda.hhs.gov]
Sent: Friday, December 23, 2016 3:30 PM
To: Webster, Debra
Subject: NDA 209777 Biopharmaceutics Information Request
Importance: High

Hello Debra,

Please respond to the following biopharmaceutics information request by COB (EST) on January 26, 2017:

1. *The release rate for all three registration batches for oxycodone ARIR (15 mg) is slower when compared to the registration batches for the 5 mg and 30 mg strengths. Provide root cause for the observed slower release of the 15 mg strength. Additionally, describe the control strategies in place to ensure that the observed difference in drug release rate does not impact in vivo performance. Alternatively, provide supportive data by using verified PBPK (physiologically-based pharmacokinetics) modeling and simulation (e.g. virtual BE (bioequivalence) study) to show that the slower release rate of a dissolution profile will not affect the bioequivalence to the RLD (ROXICODONE). For the above purpose, we recommend the following information be submitted:*

i. *A modeling summary report, which provides an overview of the modeling strategy, and details of the modeling procedures including model development, model verification/modification, and model application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.*

ii. *Detailed information on the inputs used in the construction and validation of the model(s) and simulations. All the physiological and physicochemical parameters as well as their sources should be clearly specified. It is understandable that some input parameters are estimated (optimized). However, when the parameters are optimized, the data source selection, the estimation method, the justification for the optimization algorithm, and the assumption used should be provided.*

iii. *Although the FDA does not require the use of a specific software, due to substantive differences in software/versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.*

iv. *The methodological approach to model verification, model verification results, and sensitivity analyses to evaluate the robustness of the model should be clearly presented. Note that it is generally expected that the clinical data will contribute to establish confidence in the appropriateness of the model in addressing the study question(s).*

v. *The results of using the verified model to address the study question(s) should be presented using tables, figures and text where appropriate.*

vi. *The FDA's final decision regarding the acceptability of the dissolution method and acceptance criteria (on) will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust PBPK model predictability.*

An email response will suffice initially but kindly follow this response with a formal submission to NDA 209777.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
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Please ensure that you have a secure email address for receiving confidential information. Contact the Office of Information Management (OIM) to request secure email via SecureEmail@fda.hhs.gov.

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/s/

TAIYE AYOOLA
12/28/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777 Biopharmaceutics Information Request
Date: Friday, December 23, 2016 4:29:00 PM
Importance: High

Hello Debra,

Please respond to the following biopharmaceutics information request by COB (EST) on January 26, 2017:

1. *The release rate for all three registration batches for oxycodone ARIR (15 mg) is slower when compared to the registration batches for the 5 mg and 30 mg strengths. Provide root cause for the observed slower release of the 15 mg strength. Additionally, describe the control strategies in place to ensure that the observed difference in drug release rate does not impact in vivo performance. Alternatively, provide supportive data by using verified PBPK (physiologically-based pharmacokinetics) modeling and simulation (e.g. virtual BE (bioequivalence) study) to show that the slower release rate of a dissolution profile will not affect the bioequivalence to the RLD (ROXICODONE). For the above purpose, we recommend the following information be submitted:*

    i. *A modeling summary report, which provides an overview of the modeling strategy, and details of the modeling procedures including model development, model verification/modification, and model application in a step-wise manner. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.*

    ii. *Detailed information on the inputs used in the construction and validation of the model(s) and simulations. All the physiological and physicochemical parameters as well as their sources should be clearly specified. It is understandable that some input parameters are estimated (optimized). However, when the parameters are optimized, the data source selection, the estimation method, the justification for the optimization algorithm, and the assumption used should be provided.*

    iii. *Although the FDA does not require the use of a specific software, due to substantive differences in software/versions, clear identification of software parameters is critical, which should include: name and version of the software, and (for custom modeling software) schematics of model structure and differential equations.*

    iv. *The methodological approach to model verification, model verification results, and sensitivity analyses to evaluate the robustness of the model should be clearly presented. Note that it is generally expected that the clinical data will contribute to establish confidence in the appropriateness of the model in addressing the study question(s).*

    v. *The results of using the verified model to address the study question(s)*

should be presented using tables, figures and text where appropriate.

vi. *The FDA's final decision regarding the acceptability of the dissolution method and acceptance criteria (on) will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust PBPK model predictability.*

An email response will suffice initially but kindly follow this response with a formal submission to NDA 209777.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
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/s/

TAIYE AYOOLA
12/23/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777 Information Request
Date: Friday, December 23, 2016 8:52:00 AM
Importance: High

Hello Debra,

Please respond to the following information request by COB (EST) on **Monday, January 16, 2017** and kindly follow your email submission with a formal one to your NDA 209777.

> *Table 2.7.4-4 from the Summary of Clinical Safety describes the subject disposition for the safety population. Provide definition for the safety population and explain how the number of subjects (N) from Table 2.7.4-4 (page 13) corresponds to the number of subjects categories (i.e subjects enrolled, randomized, treated, and completed study) described in Table 2.7.4-3 (page 12).*

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
12/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209777

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

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, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for RoxyBond (Oxycodone ARIR) Immediate-Release Oral Tablets, 5 mg, 15 mg, and 30 mg.

We also refer to your amendments dated November 1 and 17, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is April 21, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: *Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 31, 2017.

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

Clinical Pharmacology

1. For Study O-ARIR-003, provide a comparison of partial AUCs (point estimate and 90% confidential intervals) at all time points from time 0 to 4h (e.g., $AUC_{0\text{-}1\ h}$, $AUC_{0\text{-}1.5\ h}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}3h}$, and $AUC_{0\text{-}4h}$) between the test and the reference treatments. Provide justification that the delayed T_{max} for your product under fasted conditions compared to Roxicodone will not affect the efficacy of your product, particularly with regard to onset of action.

2. For your 505(b)(2) application, you must establish a scientific bridge to the listed drug Roxicodone. You propose that the bridge between the 30 mg strength of your product and the 30 mg strength of Roxicodone is established by the bioequivalence (BE) study evaluating these two treatments. In addition, you conducted a dose proportionality study across the 5, 15 and 30 mg strengths of your product. However, you have not conducted a BE study between the 5 and 15 mg strengths of your proposed product and Roxicodone. Provide justification for how the bridge is established between these two strengths of your product and Roxicodone.

Biopharmaceutics

3. It appears that you claim oxycodone HCl as a BCS class I drug. Clarify the regulatory purpose of this claim and provide adequate solubility and permeability data to support your claim (refer to Guidance for Industry, *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System available at:* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf).

4. Submit the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include (but not be limited to) the following information:

   a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions) used to select the proposed dissolution method as the optimal test for your product.

   b. The dissolution data (individual, mean, SD, profiles) should be reported. The testing conditions used for each test should be clearly specified.

5. Provide dissolution profiles supporting your proposed specification ranges of the identified critical material attributes and process parameters (such as (b) (4) etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. **Full Prescribing Information (FPI)**
   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)]*."
   Comment: *For example, [see Lactation (8.2)] should be [see Use in Specific Populations (8.2)] in accordance with the preferred presentation of the section heading followed by the numerical identifier.*

2. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 6, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

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/s/

SHARON H HERTZ
12/15/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Information Request
Date: Thursday, December 08, 2016 1:42:00 PM
Importance: High

Dear Dr. Webster,

Please respond to the following information request by COB (EST) on Monday, December 20, 2016:

> *Please confirm whether or not any pregnancies occurred during the clinical development program for Roxybond (oxycodone ARIR), NDA 209777. If pregnancies did occur during the clinical development program, please provide any known details about these pregnancies, including gestational age at the time of drug exposure, pregnancy outcomes (gestational age at type of birth, type of delivery, spontaneous abortion, stillbirth, etc) and fetal outcomes (fetal malformations, small-for-gestational age, etc.).*

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
12/08/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: NDA 209777: Information Request
Date: Friday, December 02, 2016 11:41:00 AM
Importance: High

Good Morning Dr. Webster,

Please respond to the following information request by **close of business (EST) Thursday, December 15, 2016** and then follow-up with an official submission to NDA 209777.

Provide a summary table for the cumulative exposure to Oxycodone ARIR and Roxicodone from all clinical studies. Present the data broken down by dose, physical manipulation state, and route of administration.

Oxycodone ARIR:

- *5 mg oral*
- *15 mg oral*
- *30 mg oral*
- *30 mg intranasal ground*

Roxicodone:

- *30 mg oral*
- *30 mg intranasal crushed*

Thank you,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
12/02/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: RE: IDS_NDA209777_Response to Information Request- Clinical Pharmacology
Date: Monday, November 14, 2016 10:16:00 AM
Attachments: image001.png

Hello Debra,

The data files for the ARIR 003 study attached to your email correspondence on November 10th, 2016 are acceptable.

Have a great day.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
FDA|WO|CDER|ODE II|DAAAP
Office: (240)-402 8561

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Thursday, November 10, 2016 4:55 PM
To: Ayoola, Taiye
Subject: IDS_NDA209777_Response to Information Request- Clinical Pharmacology

Hi Taiye,
Please find attached the requested data files for the ARIR OO3 study. This zip file has been checked for viruses and found to be virus-free. We plan on submitting these same exact files to the NDA on November 17, 2016. Please confirm receipt and acceptability of these files.
Thank you!

Regards,
Debra

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Essential to care™
Logistics
Product
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Patient

Debra Aub Webster, PhD
Principal Scientist, Regulatory Affairs and Product Development
Cardinal Health Regulatory Sciences
7400 W 110th St, Suite 300,
Overland Park, KS 66210
913.661.3881 dir | 913.451.3846 fax |
(b) (6) mobile
debra.webster@Cardinalhealth.com
www.cardinalhealth.com/regulatorysciences

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TAIYE AYOOLA
11/14/2016

From: Ayoola, Taiye
To: "Webster, Debra"
Subject: RE: NDA209777 Request for information
Date: Tuesday, November 08, 2016 2:46:00 PM
Attachments: image001.png
Importance: High

Hello Debra,

This is to confirm that we are fine with the data set that was provided for study ARIR-006 for NDA 209777. Please provide the requested data set for study ARIR-003 by the previously mentioned Friday, November 11, 2016 deadline. As stated earlier in a previous email correspondence, an initial email response will be fine but an official submission to the NDA 209777 should follow.

Thank you,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Tuesday, November 08, 2016 12:39 PM
To: Ayoola, Taiye
Subject: IDS NDA200777 Request for information

Hi Taiye,
Thank you for this additional clarification. I believe we understand what the reviewer is looking for. For study ARIR-006 we think that the information the reviewer is looking for can be found in the adpc.xpt file under the columns for ATPTN and ARELTM, which are defined in the Analysis Dataset Definition for the ADPC.xpt SAS datafile as:
ATPTN: Analysis Timepoint, which is a numeric variable derived from PC.PCTPTNUM
ARELTM: Analysis Relative Time (actual time) which is a numeric variable derived as follows: (ADTM-TRTDTM)/60/60; where
ADTM = Analysis Date/Time and TRTDTM = Date/Time of Treatment

We have confirmed that the ARIR-003 study does not have this information in the SAS data files. We will be generating the ADPC.xpt file that will contain this information and will provide this by email

by Nov 11 and will follow-up with an official submission.

If you could please confirm if this is the information you are looking for? If perhaps we are still not understanding what information you are looking for perhaps we could have a call to discuss.
Thank you for your help.

Regards,
Debra

Debra Aub Webster, PhD
Principal Scientist, Regulatory Affairs and Product Development
Cardinal Health Regulatory Sciences
7400 W 110th St, Suite 300,
Overland Park, KS 66210
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/s/

TAIYE AYOOLA
11/08/2016

From: Ayoola, Taiye
To: "debra.webster@cardinalhealth.com"
Subject: RE: NDA 209777 Information Request
Date: Monday, November 07, 2016 12:32:00 PM
Attachments: image001.png
Importance: High

Hello Dr. Webster,

We note that you have a column for Date/Time of Specimen Collection as PCDTC. However, what is being requested are the columns with the sample time (e.g., hour post dose) in numeric format. See the table below for an example of how the column should be structured.

Actual time	Planned time
0	0
X	Y

Kindly submit an official response to your NDA following your email response to the information request. The cover letter that accompanies the submission should identify the information that is being submitted, which is *Response to Information Request- Clinical Pharmacology*. Let me know if you have any additional questions.

Thanks,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

From: Webster, Debra [mailto:debra.webster@cardinalhealth.com]
Sent: Friday, November 04, 2016 1:55 PM
To: Ayoola, Taiye
Subject: RE: NDA 209777 Information Request

Hi Dr. Ayoola,

I believe, the data you are requesting is in the PC.xpt files for each of the studies. As indicated in the

In the ARIR-003 study in the Data Tabulation Data Definition file see the definition:

PCDTC	Date/Time of Specimen Collection		date	16	ISO8601	CRF Pages 26 30 42 46 58 61	

In the ARIR-006 study in the Data Tabulation Data Definition file see the definition:

PCDTC	Date/Time of Specimen Collection	datetime	ISO8601	DERIVED	Timing	See Computational Method: COMPMETHOD.PCDTC

The problem is likely because in the PC.xpt you have to expand the column width to see the actual time of blood sample collection.
Please confirm that this is the information you are looking for and whether or not this response needs to be submitted to the NDA as a general correspondence.
Let me know if there is anything else that you need.
Thank you.

Regards,
Debra

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Patient

Debra Aub Webster, PhD
Principal Scientist, Regulatory Affairs and Product Development
Cardinal Health Regulatory Sciences
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(b) (6) mobile
debra.webster@Cardinalhealth.com
www.cardinalhealth.com/regulatorysciences

From: Ayoola, Taiye [mailto:Taiye.Ayoola@fda.hhs.gov]
Sent: Friday, November 04, 2016 11:50 AM
To: Webster, Debra

Subject: NDA 209777 Information Request
Importance: High

Hello Dr. Webster,

Please respond to the following information request by COB (EST) on Friday, November 11, 2016:

For your pivotal comparative BA/BE Study O-ARIR-003 and dose proportionality Study O-ARIR-006, provide raw PK datasets that you used to calculate final PK parameters. We note that the datasets (i.e., PC) you provided in the NDA do not include actual PK sampling time points for calculating PK parameters.

An initial email response will be fine but please follow the email submission with an official submission to your NDA.

Thank you,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
11/07/2016

From: Ayoola, Taiye
To: "debra.webster@cardinalhealth.com"
Subject: NDA 209777 Information Request
Date: Friday, November 04, 2016 12:49:00 PM
Importance: High

Hello Dr. Webster,

Please respond to the following information request by COB (EST) on Friday, November 11, 2016:

For your pivotal comparative BA/BE Study O-ARIR-003 and dose proportionality Study O-ARIR-006, provide raw PK datasets that you used to calculate final PK parameters. We note that the datasets (i.e., PC) you provided in the NDA do not include actual PK sampling time points for calculating PK parameters.

An initial email response will be fine but please follow the email submission with an official submission to your NDA.

Thank you,
Taiye

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
(P) 240.402.8561
(E) Taiye.Ayoola@fda.hhs.gov

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/s/

TAIYE AYOOLA
11/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209777

NDA ACKNOWLEDGMENT

Inspirion Delivery Sciences, LLC
233 Mt Airy Rd, Ste 100
Basking Ridge, NJ 07920

Attention: Debra Aub Webster, PhD
Cardinal Health Regulatory Sciences

Dear Dr. Webster:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: RoxyBond (Oxycodone ARIR) Immediate-Release Oral Tablets 5 mg, 15 mg, and 30 mg

Date of Application: October 21, 2016

Date of Receipt: October 21, 2016

Our Reference Number: NDA 209777

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 20, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Taiye Ayoola, PharmD
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

TAIYE AYOOLA
11/01/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 105951

MEETING MINUTES

Cerovene Inc.
612 Corporate Way, Suite #10
Valley Cottage, NY 10989

Attention: Ray DiFalco
V.P. of Operations

Dear Mr. DiFalco:

Please refer to your Pre-IND file for ARIR Oxycodone.

We also refer to the meeting between representatives of your firm and the FDA on November 24, 2009. The purpose of the meeting was to discuss your development plan for ARIR Oxycodone.

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

If you have any questions, please call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

SPONSOR MEETING AGENDA

MEETING DATE/TIME: November 24, 2009/1:30 PM EST
LOCATION: 10903 New Hampshire Avenue, Silver Spring, MD; Bldg 22/Room 1313
APPLICATION: PIND 105951
STATUS OF APPLICATION: Pre-submission
PRODUCT: ARIR Oxycodone, 5-, 15-, (b) (4) and 30-mg Tablets
INDICATION: pain
SPONSOR: Cerovene Inc.
TYPE OF MEETING: Type B/Pre-IND
MEETING CHAIR: Sharon Hertz, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER: Lisa Basham, Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Sharon Hertz, MD	Deputy Director, DAARP
Ellen Fields, MD	Clinical Team Leader, DAARP
Danae Christodoulou, PhD	Pharmaceutical Assessment Lead, ONDQA
Daniela Vanco, MD	Clinical Reviewer
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Ping Ji, PhD	Clinical Pharmacology reviewer
Armaghan Emami, PhD	Pharmacology/Toxicology Reviewer
Abolade Adeolu	Regulatory Project Manager; Office of Drug Safety and Epidemiology (OSE)
Cherrye Milburn	Regulatory Project Manager, OSE
Lisa Basham, MS	Senior Regulatory Project Manager

Sponsor Attendees	Title
Ray DiFalco	Vice President of Operations, Cerovene
Manish Shah	President, Cerovene
Stefan Aigner, MD	CEO, Inspirion Delivery Technology
Kip Martin	CFO, Inspirion Delivery Technology
(b) (4)	

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-105951	GI-1	Cerovene, Inc	ARIR oxycodone immediate release tablets, 5, 15 & 30 mg

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/s/

LISA E BASHAM
02/16/2010