

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209777Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	209777/00
Applicant Name	Inspirion Delivery Sciences, LLC
Date of Submission	October 21, 2016
PDUFA Goal Date	April 21, 2017
Proprietary Name / Established (USAN) Name	RoxyBond / Oxycodone hydrochloride
Dosage Forms / Strength	Oral tablets / 5 mg, 15 mg, and 30 mg
Proposed Indication(s)	Management of moderate to severe pain where the use of an opioid analgesic is appropriate.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer/ CDTL Review	Anjelina Pokrovnichka, MD, Joshua Lloyd, MD
Pharmacology Toxicology Review	Carlic Nguyen, PhD, R Daniel Mellon, PhD
CMC Review/OBP Review	Ben Stevens, PhD, Xiaobin Shen , PhD, Tarun Mehta , PhD, Daniel DiCiero, PhD, Fang Wu, PhD, Sandra Suarez, PhD, Steven Kinsley, PhD, Ciby Abraham, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD
OSI	Shila S Nkah
OSE/DMEPA	James Schlick, MBA, RPh, Otto L. Townsend, PharmD, Vicky Borders-Hemphill, PharmD
OPDP/DCDP	L. Shenee Toombs, Olga Salis, Michael Wade,
OMP/DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN, Barbara Fuller, RN, MSN, CWOCN, Morgan Walker, PharmD, MBA, CPH
DPMH	Jane Liedtka MD, Miriam Dinatale, DO, Lynne P Yao, MD
CSS	James Tolliver PhD, Silvia Calderon, PhD
Statistical Review	Anna Sun, PhD, Qianyu Dang, PhD, Yi Tsong, PhD

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

CSS – Controlled Substance Staff

OSE= Office of Surveillance and Epidemiology

OSI=Office 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

Roxybond is a Schedule II immediate-release formulation of oxycodone hydrochloride (5, 15, and 30 mg), with excipients intended to impart physico-chemical properties that will deter some attempts at abusing Roxybond by manipulating the tablet. The proposed indication is for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The product was studied under IND 105951. The application was submitted as a 505(b)(2) application with reference to the Agency's prior findings of safety and efficacy for Roxicodone (NDA 021011; approved August 31, 2000).

2. Background

The value of an AD formulation of immediate-release oxycodone is based on the general problem of prescription opioid abuse, and the fact that as oxycodone-containing products listed under Schedule II of the Controlled Substance Act, they carry a known risk for abuse. Much has been written about the extent of prescription opioid abuse in the US. There has been a growing understanding of the need to re-evaluate the manner in which pain is managed in the US including the approach of managing chronic pain by prescribing medication in place of a coordinated interdisciplinary approach. Acute pain may often be managed by prescribing an opioid when a non-opioid analgesic may be sufficient, and greater number of tablets are often prescribed and dispensed than needed for the management of the acute pain episode. These are factors that have contributed to the widespread availability of opioids in medicine cabinets across the country.¹ This is important not only for the sake of patient safety, but for society as a whole, as the widespread availability of opioids prescribed by healthcare providers is the source for much of the misuse and abuse of opioids in the US.²

The primary route of abuse of most opioid analgesics is oral, followed by varying amounts of intranasal and intravenous abuse depending on the specific formulation or opioid. This is true for both immediate-release and extended-release products. Extended-release opioid products are often manipulated to defeat the extended-release characteristics resulting in faster release of the opioid, and an earlier and higher peak drug level when abused by the oral route. However, immediate-release products are abused most frequently by the oral route and can be abused orally without manipulation, limiting the ability of abuse-deterrent formulations intended to resist manipulation to have an impact on the overall abuse of the product. In addition, opioid

¹ <https://prevention.nih.gov/programs-events/pathways-to-prevention/recent-workshop/opioids-chronic-pain/workshop-resources>

² Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, 2012. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012. NSDUH Series H-41; HHS publication (SMA) 11-4658.

analgesics are manipulated to create material suitable for abuse by insufflation and by the intravenous route. Roxybond contains excipients intended to impart physicochemical properties that resist manipulation for the purpose of abuse. The ability of this formulation to resist manipulation has been evaluated in a series of in vitro and in vivo studies discussed in detail below. These studies represent a best effort to predict whether the formulation properties will have an impact on behavior. Note that the methodology for the in vivo studies is borrowed from the human abuse liability studies used to evaluate the abuse potential of a new drug. The important endpoints for an evaluation of abuse potential and for abuse deterrence overlap, but the focus is different. For an abuse liability assessment, the evaluation is intended to determine if the product produces a high and how much it is liked, along with many other important endpoints.³ However, the property of abuse deterrence is a relative property, and the evaluation of abuse deterrence requires comparison to either a non abuse-deterrent opioid analgesic or an abuse-deterrent opioid analgesic when available.⁴ The important endpoints in these studies are patient reported outcomes, with emphasis on drug high, drug liking, and take drug again. The critical information from the study is whether there is a difference in the likelihood that individuals will want to abuse the product were it available. Differences may be reported in the extent of drug high and drug liking, but there are no data to describe what magnitude of difference is clinically relevant and represents a deterrent effect. Therefore, subjects are asked directly whether they would take the drug again, and this endpoint is used to provide context about whether the results of drug liking or drug high are meaningful to the subject. For products that are approved with labeling describing abuse-deterrent properties, additional evaluation of the actual impact on abuse will be required in postmarketing studies.

There are nine extended-release opioid analgesic products approved with labeling describing abuse-deterrent properties consistent with the guidance for industry⁵, including four approved extended-release oxycodone products, OxyContin (oxycodone HCl extended-release tablets, NDA 022272), Targiniq (oxycodone HCl/naloxone HCl extended-release capsules), Xtampza ER (oxycodone HCl extended-release capsules), and Troxyca ER (oxycodone HCl/naltrexone HCl extended-release capsules). Oxaydo (oxycodone hydrochloride tablets, NDA 202080) is the only immediate-release opioid product with a description of data relevant to abuse-deterrence (i.e., a description of an intranasal human abuse potential study) in labeling. This labeling was approved prior to the issuance of the April 2015 abuse-deterrent guidance and is not consistent with that guidance.

The Applicant submitted a full CMC package and refers to an approved product owned by the Applicant, Morphabond ER (NDA 206544), to support the safety of excipients in Roxybond. The Applicant conducted studies to characterize the single-dose and multiple-dose pharmacokinetic characteristics of Roxybond, along with the effect of food and dose proportionality of the three strengths. The Applicant is relying on the Agency's previous findings of safety and effectiveness for Roxycodone (NDA 021011), and has not conducted any

³ See Draft Guidance for Industry, Assessment of Abuse Potential of Drugs, <http://www.fda.gov/downloads/drugs/guidances/ucm198650.pdf>

⁴ See Guidance for Industry, Abuse-deterrent Opioids – Evaluation and Labeling, <http://www.fda.gov/downloads/drugs/guidances/ucm334743.pdf>

⁵ ibid

additional efficacy or safety studies. The Applicant conducted studies to provide data on the in vitro and in vivo evaluation of the abuse-deterrent properties of Roxybond.

3. CMC//Biopharmaceutics

From the OPQ executive summary:

The drug substance, Oxycodone HCl is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 5/19/2016). Oxycodone is a white (b) (4) powder. The drug substance has a (b) (4) month retest period when stored (b) (4) at (b) (4) °C.

Roxybond IR tablets are round, coated tablets printed with (b) (4) ink. All strengths (5, 15, and 30 mg) of Roxybond are manufactured using the same manufacturing process. (b) (4)

The drug product is packaged in a 100-cc, round, white high-density polyethylene bottle with a 38-mm, white, child-resistant, induction seal closure with a 1g desiccant. An expiry of 36 months is granted for Roxybond 5 mg, 15, and 30 mg tablets when stored at 25°C (77°F); excursions permitted between 15°C-30°C (59°-86°F).

The in vitro abuse deterrent studies were found to be acceptable from a CMC perspective. The final determination of whether an abused deterrent claim will be granted in section 9.2 of the package insert will be determined by the controlled substance staff and clinical team. Additional information of the category 1 studies can be found in the Drug Product section.

The in vitro abuse deterrent studies were found to be acceptable from a CMC perspective. The final determination of whether an abused deterrent claim will be granted in section 9.2 of the package insert will be determined by the controlled substance staff and clinical team. Additional information of the category 1 studies can be found in the Drug Product section.

CMC has two Post Marketing Commitments (PMC) for the applicant. The first PMC is to conduct stability studies on small volume extractions. The purpose for this PMC is to ensure the ADF properties of the product remain stable through to expiry. The extraction and injectability studies using several solvents will be repeated yearly as part of the ongoing stability studies. The second PMC is to submit an updated in-process sampling plan and 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 purpose for this PMC is to ensure that the sponsor, in conjunction with its manufacturing facility, develops a statistically relevant sampling plan for stratified (b) (4) of the (b) (4) coated tablets to ensure product meeting the acceptance criteria in the sampling plan will conform to the critical quality attributes of the drug product with a high degree of statistical confidence to inform on the quality of the entire manufactured batch. Below are the PMC's sent and agreed upon by the applicant.

PMC:

Drug Product

1. 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 the same study conditions in the completed in vitro studies submitted to the NDA, to demonstrate that there is no change in the in extraction recovery in the drug product stored over time. Commit to repeating these studies yearly.

Facilities

2. The sponsor commits to submit 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 abuse-deterrent properties of Roxybond are based on a unique design. As described in the Drug Product review, (b) (4)



I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance and with the agreed upon postmarketing commitments. Stability testing supports an expiry of 36 months. There are no outstanding issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology review:

No nonclinical studies were required to be submitted to support this 505(b)(2) application for oxycodone hydrochloride. There were no nonclinical studies submitted with oxycodone hydrochloride for primary and secondary pharmacology, safety pharmacology, ADME, toxicokinetics, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology, and special toxicology studies. There were no nonclinical safety concerns with the drug substance or drug product specifications or the container closure system as the proposed drug product is formulated as solid oral tablets. The Applicant is cross-referencing Morphabond ER (NDA 206544) for the safety of the excipients used in the formulation as RoxyBond and Morphabond share several excipients. There are no safety issues precluding approval for the excipients used in Roxybond. The Applicant's proposed language in the Impairment of Fertility section of the label is not acceptable. Although not an approval issue in this NDA, post-marketing requirements (PMRs) were issued to Inspirion (now Daiichi-Sankyo) for Morphabond to conduct toxicology studies in order to qualify the safety of the (b) (4). These should also be issued to Inspirion for this NDA as well. These toxicology studies include both the 6- and 9-month repeat-dose toxicology studies in rodent and nonrodent species with (b) (4) respectively, as well as the 2-year carcinogenicity assessment with (b) (4).

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

From the Clinical Pharmacology addendum:

This is an addendum to the original clinical pharmacology review in DARRTS dated 3/22/2017. OSI memorandums dated February 27, 2017 (for analytical site) and March 26, 2017 (for clinical site) recommended accepting the pharmacokinetic data obtained from the pivotal comparative BA/BE Study O-ARIR-003. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated October 21, 2016 and January 31, 2017 and finds it acceptable provided that a mutual agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

The clinical pharmacology evaluation was summarized in the advisory committee background, and is reproduced here, verbatim:

The proposed indication for RoxyBond (oxycodone hydrochloride) immediate-release tablets is for the management of moderate-to-severe pain where the use of an opioid analgesic is appropriate. The safety and efficacy of RoxyBond is based on the demonstration of bioequivalence to the listed drug Roxicodone (NDA 021011) for this 505(b)(2) New Drug Application. The clinical program for RoxyBond consisted of four Phase 1 pharmacokinetic studies and one intranasal human abuse liability (HAL) study. Efficacy studies were not required for this NDA application. The safety information

collected in the pharmacokinetic studies was of limited value due to the fact that these were single-dose studies conducted in healthy volunteers who were naltrexone- blocked. The HAL study investigated the effects of intranasal administration of manipulated RoxyBond in opioid-experienced subjects. No new safety signals were identified during the review of the RoxyBond application beyond what is already known for oxycodone.

The clinical pharmacology review focuses on two pivotal comparative bioavailability and dose proportionality studies (O-ARIR-003 and O-ARIR-006) using the to-be-marketed commercial formulation. Both studies were randomized, open-label, crossover studies conducted in healthy volunteers under naltrexone blockade. Study 003 assessed the comparative bioavailability of 30 mg RoxyBond tablets and 30 mg Roxicodone tablets under fasting condition and the food effect for the 30 mg RoxyBond tablet. Study 006 assessed dose proportionality using 5, 15, and 30 mg RoxyBond tablets under fasting conditions. Pharmacokinetic results of comparative bioavailability, food effect and dose proportionality obtained from these two studies are summarized as follows:

Comparative Bioavailability between RoxyBond Tablet and Roxicodone Tablet: RoxyBond tablet (1 x 30 mg) showed equivalent AUCt and AUCinf values, similar Cmax values, and slightly longer median Tmax values (1.8 hour for RoxyBond vs 1.0 hour for Roxicodone) in comparison to Roxicodone tablet (1 x 30 mg) under fasting condition. The oxycodone PK parameters for 30 mg RoxyBond Tablet and 30 mg Roxicodone Tablet under fasting conditions are listed below.

Table 1: Oxycodone Pharmacokinetic Parameters for 30 mg RoxyBond Tablet (also known as O-ARIR) Fasted versus 30 mg Roxicodone Tablet Fasted

Parameter	Unit	O-ARIR (Fasted) ^a (N = 58)	Roxicodone (Fasted) ^a (N = 54)
AUC _{0-t}	ng•hr/mL	287.4 (22.9)	300.3 (22.9)
AUC _{0-inf}	ng•hr/mL	292.7 (23.0)	305.4 (22.9)
C _{max}	ng/mL	57.8 (31.1)	67.7 (35.1)
T _{max}	hr	1.8 (0.8, 5.0) ^b	1.0 (0.5, 5.0) ^b
K _{el}	hr ⁻¹	0.1871 (0.1112, 0.2840) ^c	0.1932 (0.1322, 0.3117) ^c
T _{1/2}	hr	3.8 (2.4, 6.2) ^c	3.7 (2.2, 5.2) ^c

^a Values are arithmetic means (%CV)

^b Median (Range)

^c Range

The total exposures of oxycodone (AUCt and AUCinf) for 30 mg RoxyBond tablet and 30 mg Roxicodone tablet met bioequivalence (BE) criteria. The point estimate of the geometric mean ratio (RoxyBond tablet /Roxicodone tablet) for oxycodone AUCt and AUCinf were 95.6% and 95.8%, respectively. The corresponding 90% confidence intervals (CIs) were 92.5 – 98.7% and 92.8 – 98.9%, respectively. All of these 90% CIs fell within the 80 - 125% BE limit.

Oxycodone Cmax values were similar for 30 mg RoxyBond tablet and 30 mg Roxicodone tablet. The point estimate of the geometric mean ratio (RoxyBond tablet /Roxicodone tablet) for oxycodone Cmax was 86.2% and the corresponding 90% CI was 78.8% - 94.3%. The lower limit of the 90% CI for Cmax of 78.8% is very close to the

80% limit BE criterion and RoxyBond will be titrated. Therefore, a 1.2% lower CI for oxycodone C_{max} is not anticipated to affect the efficacy of RoxyBond to a substantial degree. Median (min, max) T_{max} values were 1.8 (0.8, 5.0) hours for RoxyBond tablet and 1.0 (0.5, 5.0) hour for Roxicodone tablet; RoxyBond had slightly longer median T_{max} value than Roxicodone but the range for T_{max} was similar between the two products. Considering food caused a delay in T_{max} (1.25 to 2.54 hour) for Roxicodone and there is no food restriction for Roxicodone administration, the slightly longer median T_{max} value for RoxyBond under fasting condition will not be anticipated to affect the efficacy of RoxyBond to a substantial degree.

Food Effect: The oxycodone PK parameters for RoxyBond Tablet (1x 30 mg) under fasting and fed conditions are listed below.

Table 2: Oxycodone Pharmacokinetic Parameters for 30 mg RoxyBond Tablet (also known as O-ARIR) Fed versus 30 mg RoxyBond Tablet Fasted

Parameter	Unit	O-ARIR (Fed) ^a (N = 58)	O-ARIR (Fasted) ^a (N = 58)
AUC _{0-t}	ng•hr/mL	354.2 (23.3%)	287.4 (22.9%)
AUC _{0-inf}	ng•hr/mL	361.9 (23.9%)	292.7 (23.0%)
C _{max}	ng/mL	68.0 (29.5%)	57.8 (31.1%)
T _{max}	hr	2.0 (1.0, 6.1) ^b	1.8 (0.8, 5.0) ^b
K _{el}	hr ⁻¹	0.1824 (0.1204, 0.2810) ^c	0.1871 (0.1112, 0.2840) ^c
T _{1/2}	hr	3.9 (2.5, 5.8) ^c	3.8 (2.4, 6.2) ^c

^a Values are arithmetic means (%CV)

^b Median (Range)

^c Range

A high-fat meal increased oxycodone C_{max}, AUC_t, and AUC_{inf} values by 18%, 23%, and 24%, respectively, following the administration of a single dose of 30 mg RoxyBond tablet. Median (min, max) T_{max} values were similar under fasting and fed conditions; 1.8 (0.8, 5.0) hours under fasting and 2.0 (1.0, 6.1) hours under fed condition. The food effect on oxycodone AUC for RoxyBond tablet is similar to that for Roxicodone, the identified listed drug for this 505(b)(2) NDA. According to the approved Roxicodone labeling, a high fat meal enhanced the extent of absorption (27% increase in AUC). In addition, food caused a delay in T_{max} (1.25 to 2.54 hours). Roxicodone labeling does not recommend a food restriction because of the limited extent of the food effect. Therefore, a food restriction should not be recommended for RoxyBond tablet either.

Dose Proportionality: Following a single dose administration of RoxyBond 5, 15, and 30 mg tablets to healthy volunteers under naltrexone block and fasting conditions, oxycodone C_{max} and AUC values were dose proportional based on the analyses on log transformed parameters using a power model. The slopes of log-transformed C_{max}, AUC_t, and AUC_{inf} values for oxycodone were 0.9769, 1.0081 and 0.9799, respectively, and they fell within the range of 0.80 to 1.25. In addition, the 90% CIs around the slope were within the predefined boundary (0.8755, 1.1245). Therefore, dose proportionality is demonstrated over the range of 5 mg to 30 mg for RoxyBond. As described in its label, dose proportionality was also demonstrated for Roxicodone tablets.

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

Not applicable.

7. Clinical/Statistical-Efficacy

No new clinical efficacy studies were submitted in support of this application. The exposure to oxycodone following dosing with RoxyBond is comparable to Roxicodone, based on relative bioavailability data, and the intended patient population is the same. Therefore, there is an adequate scientific bridge to rely in the agency's previous finding of effectiveness for Roxicodone to support the efficacy of RoxyBond.

8. Safety

No new clinical safety studies were submitted in support of this application. The exposure to oxycodone following dosing with RoxyBond is comparable to Roxicodone, based on relative bioavailability data, and the intended patient population is the same. Therefore, there is an adequate scientific bridge to rely in the agency's previous finding of safety for Roxicodone to support the safety of RoxyBond.

The Applicant conducted four Phase 1 pharmacokinetic (PK) studies and one intranasal human abuse potential (HAP) study with the final-to-be-marketed formulation. The safety data from the PK studies were based on single-dose administration in healthy volunteers under naltrexone-blockade and are of limited value other than to demonstrate that there were not any issues with swallowing the formulation due to the [REDACTED] (b) (4). The HAP study investigated the effects of intranasal administration of manipulated RoxyBond in opioid-experienced subjects. Dr. Pokrovnichka reviewed the safety data and found no unusual adverse events among the 366 subjects were exposed to the final to-be-marketed formulation of RoxyBond in the PK and HAP studies. There were no deaths or serious adverse events.

9. Advisory Committee Meeting

A the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, held on April 5, 2017. The following is a summary of the discussion and votes based on the questions posed to the committee members.

1. **DISCUSSION:** Please discuss whether there are sufficient data to support a finding that RoxyBond (oxycodone hydrochloride immediate-release tablets) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the following routes of abuse:

- a. Nasal
- b. Intravenous

Committee Discussion: The majority of the committee concurred that there is sufficient data to support a finding that RoxyBond has properties that can be expected to deter abuse by the intravenous and nasal routes. The committee agreed that the abuse-deterrent physiochemical properties designed to deter both nasal and intravenous abuse; the in vitro results demonstrating decreased potential for manipulation, extraction, and syringeability; and the results from the intranasal human abuse potential study demonstrating decreased drug liking and willingness to take the drug again supported this finding. Several committee members mentioned that they were concerned with the lack of data surrounding injury potential when injecting the excipients in this product and encouraged the Agency and the Applicant to consider this. Please see the transcript for details of the committee discussion.

2. **VOTE:** If approved, should RoxyBond be labeled as an abuse-deterrent product by the nasal route of abuse?

Vote Result: Yes: 19 No: 1 Abstain: 0

Committee Discussion: The majority of the committee voted “Yes,” agreeing that RoxyBond should be labeled as an abuse-deterrent product by the nasal route of abuse if approved. These committee members stated that, on the whole, the pharmacokinetic and pharmacodynamic data provided were compelling and showed that the product will make it more difficult for some people to abuse it. The committee member who voted “No” stated that the definition of abuse deterrence was unclear. Please see the transcript for details of the committee discussion.

3. **VOTE:** If approved, should RoxyBond be labeled as an abuse-deterrent product by the intravenous route of abuse?

Vote Result: Yes: 16 No: 4 Abstain: 0

Committee Discussion: The majority of the committee voted “Yes,” agreeing that RoxyBond should be labeled as an abuse-deterrent product by the intravenous route of abuse if approved. These committee members stated that the in vitro data, drug dissolution data, gelling properties of the product, and large injection volume necessary were convincing factors in their vote. Many committee members stated that they would like to see a warning of some sort about the lack of knowledge surrounding possible outcomes of injecting the product’s excipients. One of the committee members who voted “No” stated that the intravenous abuse-deterrent steps were relatively easy to accomplish. Other committee members who voted “No” opined that they were worried about the unknown risks of injecting the product’s excipients. Please see the transcript for details of the committee discussion.

4. **VOTE:** Should RoxyBond be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

Vote Result: Yes: 19 No: 0 Abstain: 1

Committee Discussion: The majority of the committee voted “Yes,” that RoxyBond should be approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. These committee members stated that this product shows an incremental advantage in abuse-deterrence and meets an important public health need. Some committee members stated that they support approval of this product with clear labeling describing the abuse-deterrent studies so that prescribers can decide who is a proper candidate for this abuse-deterrent formulation versus available non-abuse-deterrent formulations. Several committee members encouraged the Agency and Applicant to explore the use of this product in children. The committee member who abstained from voting stated that having another abuse-deterrent formulation on the market will just detract from addressing the opioid epidemic, even if RoxyBond isn't labeled as an abuse-deterrent formulation, as it is still formulated as such. Please see the transcript for details of the committee discussion.

10. Pediatrics

RoxyBond does not represent a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, and, therefore, does not trigger the requirements under PREA.

11. Other Relevant Regulatory Issues

Abuse Deterrence

The following has been reproduced from the clinical review, verbatim:

In Vitro Study Results

Among the in vitro abuse-deterrent studies conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties, only the methodologies that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below.

The Applicant evaluated the in vitro abuse-deterrent characteristics of RoxyBond by conducting studies to assess physical manipulation using household tools, large volume extraction, and syringeability and small volume extraction. The highest strength of RoxyBond (30 mg) was used for the in vitro testing, with the 30 mg strength of Roxycodone as the comparator.

The Applicant conducted a study to evaluate the physical manipulation of RoxyBond using household tools, including a cheese grater, coffee grinder, hammer, knife, mortar and pestle, pill crusher, and spoon. The ability to reduce particle size using these tools was evaluated with and without pre-treatment with freezing at $\leq 0^{\circ}$ C for 30 minutes, microwaving for 1 minute (800 W), or heating in a 150° C oven for 30 minutes. The agency requested evaluation of additional pretreatment conditions, including higher power microwaving for various durations.

Roxicodone was easily crushed into a fine powder suitable for insufflation using a glass pestle; Roxicodone did not provide any abuse-deterrent effects to physical manipulation. For RoxyBond, the coffee grinder was the only household tool tested that produced a powder suitable for insufflation. Increasing the grinding time (up to 10 minutes) did not substantially change the particle size distribution profile. The pretreatments did not meaningfully impact the results for any of the tools evaluated.

Large volume extraction studies were conducted using intact and crushed⁶ samples in 30 ml of various solvents, including water, pH buffered solutions (pH 2, pH 4, pH 6, and pH 10), methanol, isopropyl alcohol, acetone, and ethanol (20%, 40%, and 100%). Solvents were evaluated at room temperature and 90° C,⁷ with and without agitation at 100 rpm. Water and the pH buffered solutions were evaluated over 1, 5, 15, 30, and 60 minute time points. In contrast, the remaining solvents were evaluated at a fixed 30-minute time point. The effects of microwaving and extraction of oxycodone from the tablet ^{(b) (4)} [REDACTED] Roxicodone was easily extracted in water, which was further enhanced by crushing and increasing temperatures. Therefore, the Applicant did not evaluate additional solvents with Roxicodone.

The results of the large volume extraction studies demonstrated that oxycodone was most efficiently extracted from RoxyBond in low pH solvents and with high temperatures and agitation. The table below represents extraction of oxycodone from RoxyBond, expressed as mean percentage label claim (%LC), in low pH solvents. Crushing increased the extraction of oxycodone at the earlier time points; however, starting at 15 minutes and beyond, grinding slowed down extraction compared to intact tablets.

Manipulated Roxicodone was easily drawn into a syringe in all tested volumes and conditions, recovering over 92% of oxycodone within 1 minute. In contrast, powder from manipulated Oxycodone ARIR tablets formed a material that was difficult to syringe and only produced a small amount of injectable liquid. The recoveries ranged from 2.5 to 18.9%, regardless of needle gauge. Doubling the number of tablets per sample was as easy to syringe the Roxicodone samples but it resulted in slightly lower recoveries ranging from 85 to 91%. But it was more difficult to syringe the Oxycodone ARIR samples and the recoveries were even lower than single tablet sample. When extracted at elevated temperature, the oxycodone recovery increased but still at not more than 33%.

⁶ The large volume extraction studies utilized a coffee grinder for RoxyBond and a mortar and pestle for Roxicodone for the purposes of crushing the samples

⁷ Volatile solvents were evaluated at room temperature only

⁸ [REDACTED] ^{(b) (4)}

In Vivo Study Results

As summarized in the clinical review, reproduced verbatim:

The Applicant additionally conducted an intranasal human abuse potential study (Study O-ARIR-002) to evaluate the abuse-deterrent effects of RoxyBond for the intranasal route. The study was a randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover study to determine the relative pharmacokinetics, pharmacodynamic (PD) effects, and safety of RoxyBond compared with Roxycodone when physically manipulated⁹ and administered intranasally to recreational, nondependent opioid users. Subjects were randomized and received the following treatments:

- Placebo Intranasal + Oral Placebo
- Crushed 30 mg Roxycodone Intranasal + Oral Placebo
- Ground 30 mg RoxyBond Intranasal + Oral Placebo
- Intact RoxyBond 30 mg Oral + Intranasal Placebo

The primary PD endpoint was Drug Liking, which was assessed using a bipolar visual analog scale (VAS) with the primary comparison between crushed Roxycodone and ground RoxyBond administered intranasally. Additional secondary PD endpoints included Drug High on a unipolar VAS, Take Drug Again on a bipolar VAS, and Overall Drug Liking on a bipolar VAS. PD measures included Emax (maximum (peak) effect) and TEmax (time to achieve Emax) among others.

Thirty-one subjects entered the treatment phase with 29 completers (2 subjects withdrew due to family emergencies).

The pharmacokinetic results are summarized in the table below:

Plasma Oxycodone Pharmacokinetic Parameter	Statistical Parameter	Active Treatments		
		RoxyBond 30 mg Intact, Oral	RoxyBond 30 mg Intranasal	Roxycodone 30 mg Intranasal
Cmax (ng/mL)	Mean (SD)	58.4 (13.1)	42.7 (13.5)	56.5 (11.5)
Tmax (hours)	Median (Range)	1.3 (0.6, 3.1)	2.3 (1.1, 4.1)	1.7 (0.6, 6.1)
AUC1hour (ng*hr/mL)	Mean (SD)	18.5 (11.2)	17.0 (7.9)	30.8 (7.6)

Source: Dr. Tolliver's review, pg. 22

Intranasal RoxyBond produced a significantly ($p < 0.0001$) lower Emax of Drug Liking than intranasal Roxycodone. However, the Emax of Drug Liking for RoxyBond was higher than that of placebo. Results for Emax of Drug Liking are summarized below:

⁹ RoxyBond – ground with a coffee grinder; Roxycodone – crushed with a mortar and pestle

VAS	Treatment (IN – Intranasal)	Mean	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Drug Liking	Placebo IN	53.41	6.34	50.00	50.00	51.00	52.00	77.00
	Roxicodone 30 mg IN	82.86	11.55	50.00	79.00	82.00	91.00	100.00
	RoxyBond 30 mg IN	71.14	12.01	50.00	65.00	71.00	78.00	100.00
	Intact RoxyBond 30 mg Oral	81.48	11.49	56.00	75.00	82.00	89.00	100.00

Source: Dr. Tolliver’s review, pg. 23

Intranasal RoxyBond produced a lower Emax of Take Drug Again compared to intranasal Roxicodone. Results for Emax of Take Drug Again are summarized below:

VAS	Treatment	Mean Emax	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Take Drug Again	Placebo IN	41.86	20.09	0.00	49.00	50.00	50.00	78.00
	Roxicodone 30 mg IN	82.14	16.44	37.00	73.00	86.00	95.00	100.00
	RoxyBond 30 mg IN	62.24	24.51	3.00	50.00	62.00	81.00	99.00
	Intact RoxyBond 30 mg Oral	77.31	18.11	13.00	70.00	81.00	89.00	100.00

Source: Dr. Tolliver’s review, pg. 26

Results for Emax of Drug High are summarized below:

VAS	Treatment (IN – Intranasal)	Mean	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Unipolar High	Placebo IN	7.52	14.93	0.00	0.00	1.00	5.00	57.00
	Roxicodone 30 mg IN	66.34	25.69	0.00	56.00	74.00	84.00	96.00
	RoxyBond 30 mg IN	39.38	25.88	0.00	18.00	40.00	57.00	100.00
	Intact RoxyBond 30 mg Oral	66.66	25.92	1.00	49.00	72.00	85.00	100.00

Source: Dr. Tolliver’s review, pg. 24

Results for Emax of Overall Drug Liking are summarized below:

VAS	Treatment (IN = Intranasal)	Mean Emax	Standard Deviation	Minimum	First Quartile	Median	Third Quartile	Maximum
Bipolar Overall Drug Liking	Ground Placebo IN	47.59	15.73	0.00	50.00	50.00	50.00	85.00
	Roxicodone 30 mg IN	80.86	14.60	35.00	73.00	85.00	90.00	100.00
	RoxyBond 30 mg IN	64.21	21.64	4.00	52.00	70.00	77.00	99.00
	Intact RoxyBond 30 mg Oral	78.55	17.41	13.00	73.00	83.00	89.00	100.00

Source: Dr. Tolliver’s review, pg. 27

The pharmacokinetic and pharmacodynamic results described above support an abuse-deterrent effect of RoxyBond for the intranasal route. Dr. Tolliver noted that “RoxyBond tablets do not display a deterrent effect to oral abuse and may, following approval, be expected to be orally abused, as subjects in [the human abuse potential study] reported similar scores of subjective measures and shorter time to peak effects

when taking intact RoxyBond to those reported when taking crushed Roxicodone intranasally.”

The CMC and CSS reviewers concluded that the results of the in vitro studies suggest that RoxyBond is more difficult to prepare for intravenous and intranasal abuse as compared to Roxicodone. The CSS reviewers determined that the results of the in vitro and in vivo abuse-deterrent studies support potential abuse-deterrent effects of RoxyBond for the intravenous and intranasal routes. However, abuse by these routes may still occur.

To summarize, the in vitro assessments demonstrated attempts to manipulate for the purpose of extraction and for the purpose of creating material suitable to inject through a syringe were substantially less successful with Roxybond than Roxicodone. In a human abuse potential study, intranasal Roxybond produced less reinforcing effects than Roxicodone.

While the abuse of immediate-release oxycodone is primarily oral, the potential to deter some amount of nasal and intravenous abuse is beneficial from the public health perspective. However, Roxybond delivers oxycodone and is, therefore, still potentially addictive and can still be abused and misused. The Applicant has agreed to conduct postmarketing studies to evaluate the effects of the abuse-deterrent properties postmarketing.

Clinical Site Inspection

The site where the intranasal human abuse potential study was conducted was not inspected as the investigator (Dr. Lynn Webster) and site have been inspected on two recent occasions for similarly conducted studies (b) (4) where no issues were identified.

Financial Disclosure – there were no concerns with the information provided and there were no financial incentives considered to adversely affect the integrity of the data.

There are no other unresolved relevant regulatory issues

12. Labeling

The proprietary name RoxyBond was reviewed and found acceptable. The package insert, medication guide, and carton and container labeling was reviewed and comments were implemented. Recommendations from DPMH for PLLR labeling were incorporated. The package insert will convey the results of the in vitro and in vivo testing of the abuse-deterrent properties of Roxybond.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

The Applicant has demonstrated that Roxybond has properties that can be expected to make manipulation for abuse by the intravenous and nasal routes more difficult than a non abuse-deterrent formulation of immediate-release oxycodone tablets. This may help deter some individuals from pursuing these routes of abuse that are generally riskier than oral abuse. However, oral abuse is the most common route of abuse for an immediate-release opioid and there is no reason to expect this formulation will not be abused orally, and for the highly motivated individual, nasal and IV abuse remain possible. At the advisory committee meeting, concern was expressed that the toxicity resulting from injection of the excipients that make Roxybond abuse deterrent may be worse than the toxicity with existing non-abuse-deterrent formulations. Toxicology studies of the excipients injected intravenously have not been conducted, nor has the amount of excipients been assessed during the extractions studies. This is a difficult situation to assess for a few reasons. First, toxicology studies generally push the dose of the study drug until toxicity is seen. If in spite of very high doses, the excipients do not cause toxicity, that may provide a measure of relief, but if toxicity is seen, it can be difficult to determine the relevance. More challenging is trying to anticipate all the ways an individual might try to defeat the abuse-deterrent features, as the experience with Opana ER, discussed at the March 13 and 14, 2017 Advisory Committee, demonstrated. The product label, in Section 9.2 does describe some of the known harms associated with intravenous abuse of drugs and also states that all of the possible toxicities may not be known.

- Recommendation for Postmarketing Risk Management Activities

The following PMRs are based on the Applicant's reference to their product, Morphabond, which was approved with the same PMRs in place:

- 3204-1 Conduct a 9-month repeat-dose oral toxicology study in the nonrodent model characterizing the toxicological potential of (b) (4)
- 3204-2 Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of (b) (4)
- 3204-3 Conduct a 2-year rodent oral carcinogenicity assessment of (b) (4)

The following PMRs are to evaluate the effect of the abuse-deterrent properties of Roxybond:

- 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.

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*.

- Recommendation for other Postmarketing Study Commitments

The following PMCs are based on the findings of the OPQ and Office of Compliance teams:

- 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.

- 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.

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