CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209777Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209777
Supporting document/s:	SDN 1, 7, and 13
Applicant's letter date:	October 21, 2016 (SDN 1), January 18, 2017 (SDN 7), and March 6, 2017 (SDN 13)
CDER stamp date:	October 21, 2016 (SDN 1), January 18, 2017 (SDN 7), and March 6, 2017 (SDN 13)
Product:	RoxyBond™, Oxycodone ARIR Tablets
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate
Applicant:	Inspirion Delivery Sciences LLC
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Supervisor:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Taiye Ayoola

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

The Applicant, Inspirion Delivery Sciences LLC, has developed an abuse-resistant immediate-release formulation of oxycodone hydrochloride called RoxyBond™ (Oxycodone ARIR) for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The Applicant has submitted a 505(b)(2) application relying upon the Agency's previous finding of safety for ROXICODNE® (NDA 21011). Cross reference is also made to Morphabond™ ER (NDA 206544) via letter of authorization from Daiichi-Sankyo permitting FDA to reference all relevant quality and preclinical toxicology and pharmacology information submitted to NDA 206544 to support this application.

1.2 Brief Discussion of Nonclinical Findings

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)

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, the proposed drug product, oxycodone hydrochloride ARIR, may be approved with the recommended labeling changes and post-marketing requirements.

1.3.2 Additional Non Clinical Recommendations

Consistent with the PMRs issued to Inspirion for Morphabond™, complete the following studies as PMRs:

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

1.3.3 Labeling

The following labeling changes are recommended:

Applicant's proposed labeling	***Reviewer's proposed changes***	***Rationale for changes***
INDICATIONS AND USAGE (b) (6)	**INDICATIONS AND USAGE**	No changes are necessary as the correct Established Pharmacologic Class for oxycodone was used and is identical to ROXICODONE®.
8.1 Pregnancy **Risk Summary** Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. (b) (4) Animal reproduction studies with oral administrations of oxycodone HCl in rats and rabbits during the period of organogenesis at doses 2.6 and 8.1 times, respectively, the human dose of 60 mg/day did not reveal evidence of	**8.1 Pregnancy** **Risk Summary** Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. (b) (4) Animal reproduction studies with oral administrations of oxycodone HCl in rats and rabbits during the period of organogenesis at doses 2.6 and 8.1 times, respectively, the human dose of 60 mg/day did not reveal evidence of	These sections were converted to the Pregnancy and Lactation Labeling Rule (PLLR) format in December of 2016 for Roxicodone in conjunction with a safety labeling change. No changes to the Roxicodone labeling should be made. The Sponsor's proposed labeling should be reverted back to the existing information in Roxicodone. See Maternal Health Consult for human risk summary statement. No changes to the Animal Risk summary statement are necessary.

teratogenicity or embryo-fetal toxicity. In several published studies, treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.	teratogenicity or embryo-fetal toxicity. In several published studies, treatment of pregnant rats with oxycodone at clinically relevant doses and below, resulted in neurobehavioral effects in offspring [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.	Standard language.
Data *Animal Data* In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up to 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 2.6 and 8.1 times an adult human dose of 60 mg/day, respectively, on a mg/m^2 basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit	Data *Animal Data* In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of oxycodone HCl administered during the period of organogenesis up to 16 mg/kg/day and up to 25 mg/kg/day, respectively. These studies revealed no evidence of teratogenicity or embryo-fetal toxicity due to oxycodone. The highest doses tested in rats and rabbits were equivalent to approximately 2.6 and 8.1 times an adult human dose of 60 mg/day, respectively, on a mg/m^2 basis. In published studies, offspring of pregnant rats administered oxycodone during gestation have been reported to exhibit neurobehavioral effects	No changes are necessary.

neurobehavioral effects including altered stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3-times an adult human dose of 60 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m^2 basis).	including altered stress responses, increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3-times an adult human dose of 60 mg/day, on a mg/m^2 basis) and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human dose of 60 mg/day, on a mg/m^2 basis).	
8.3 Females and Males of Reproductive Potential **Infertility** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2) and Nonclinical Toxicology (13.1)].*	**8.3 Females and Males of Reproductive Potential** **Infertility** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2) ~~and Nonclinical Toxicology (13.1)~~].*	
(b) (4)		(b) (4) The information contained in this reference is not adequate for inclusion in the label.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility **Carcinogenesis** Long-term studies have not been performed in animals to	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** Long-term studies have not been performed in animals to evaluate	The (b) (4) reference should be deleted. We cannot do carcinogenicity

evaluate the carcinogenic potential of (b) (4) oxycodone.	the carcinogenic potential of (b) (4) oxycodone.	studies on the (b) (6) in rodents.
Mutagenesis Oxycodone hydrochloride was genotoxic in an in vitro mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).	**Mutagenesis** Oxycodone hydrochloride was genotoxic in an in vitro mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an in vitro bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).	No changes were necessary to the mutagenesis section as it is identical to ROXICODONE®.
Impairment of Fertility (b) (4)	**Impairment of Fertility** (b) (4) Studies in animals to evaluate the potential impact of oxycodone on fertility have not been conducted.	Sponsor's proposed language. (b) (4) The information contained in this reference is not appropriate for inclusion in the label. The Impairment of Fertility section has been reverted back to that of the referenced product ROXICODONE®.

2 Drug Information

2.1 Drug

CAS Registry Number
124-90-3

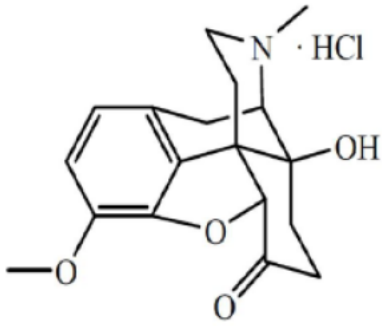
Generic Name
Oxycodone hydrochloride

Code Name
(b) (4)

Chemical Name
(5α)-4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride (9CI)

Molecular Formula/Molecular Weight
$C_{18}H_{21}NO_4$ HCl / 351.82 g/mol

Structure or Biochemical Description



Pharmacologic Class
Opioid Agonist (Established Pharmacologic Class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA#	Drug Name	Division	Strength (route)	Marketing Status	AP Date	Indication	Sponsor
21011	Roxicodone® (Oxycodone Hydrochloride)	DAAAP	5, 15, and 30 mg (oral tablet)	Approved	August 31, 2000	Management of moderate to severe pain where use of an opioid analgesic is appropriate.	Mallinckrodt Inc.
21201	Asclera (polidocanol) injection*	DCRP	0.5% and 1% solution	Approved	March 30, 2010	Varicose veins of the lower extremities	Merz Pharmaceuticals LLC
206544	Morphabond™ ER (Morphine Sulfate)	DAAAP	15, 30, 60, and 100 mg (oral tablet)	Approved	October 2, 2015	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	Daiichi Sankyo Inc.

*The Asclera NDA was listed as a referenced drug to support the safety of an excipient in this formulation. The excipient is also in Morphabond™, a cross-referenced NDA.

IND#	Drug Name	Division	Status	Indication	Sponsor
105951	Oxycodone Hydrochloride	DAAAP	Active	Treatment of moderate to severe pain.	Inspirion Delivery Sciences LLC

MF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
		(b) (4)	February 23, 2010	LOA provided. Deemed adequate for two ANDA products to date (see latest quality review dated May 19, 2016).

(b) (4)	February 8, 1977	LOA provided. The MF contains the same toxicology studies of (b) (4) (b) (4) as submitted with the NDA. (b) (4) is deemed adequate in chronic use oral products for a human dose up to (b) (4) mg/m² (see nonclinical review dated July 6, 2016).
	January 9, 2014	LOA provided. There are a number of FDA-approved oral products containing (b) (4)
	September 7, 2007	LOA provided. The individual components of each colorant used are justified (see formulation below).

2.3 Drug Formulation

The proposed drug product is a smooth surface tablet that the Applicant expects (b) (4) Although the Applicant supports this supposition through in vitro dissolution data (b) (4) in vivo data in animals or humans have not been provided. (b) (4) (see figure 1 below, from the Applicant's submission).

Figure 1: Design of the Oxycodone ARIR Tablet

(b) (4)

The following table illustrates the composition of the oxycodone ARIR tablets (data from the Applicant's submission):

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(b) (4)

2.4 Comments on Novel Excipients

As with any opioid drug product indicated for chronic use, there is no maximum daily dose listed in the proposed labeling due to the development of tolerance. The development of tolerance necessitates increased doses with time to order to obtain the same desired effect. To establish the safety of the product for opioid-tolerant individuals, the DAAAP has established a "maximum theoretical daily dose (MTDD)" of (b) (4) mg per day as the MTDD via (b) (4) tablets of the 30 mg ARIR tablets for immediate-release oxycodone products dosed 4-6 times a day.

The following table illustrates the amount of each excipient at the Maximum Theoretical Daily Dose (MTDD) of (b) (4) tablets of oxycodone hydrochloride via the 30 mg ARIR tablets and compares the levels to the maximum potency data from the FDA CDER Inactive Ingredients Database (IID):

Table 2: Maximum Daily Levels of the Excipients

Excipient	Maximum Potency in Approved Chronic Oral Products via the FDA IID (mg/dosage form)	Amount at the MTDD ((b) (4) tablets) using the 30 mg ARIR tablets (mg)	Coverage Up To the MTDD via IID
Hypromellose (b) (4)	(b) (4)		
Xanthan gum (b) (4)			
Microcrystalline cellulose (b) (4)			
Sodium alginate			
Alginic acid			
Mannitol (b) (4)			
Colloidal silicon dioxide (b) (4)			
Magnesium stearate			
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)			
Lactose monohydrate (b) (4)			

(b) (4)	(b) (4)
Polysorbate 80	
(b) (4)	
(b) (4)	
Ethylcellulose	
Dibutyl sebacate	
(b) (4) coating for 30 mg tablet	
Polyvinyl alcohol,	
Titanium dioxide[a,d]	
Polyethylene glycol[a]	
Talc[a]	
FD&C Blue #2/	
Iron oxide yellow[a,g]	
(b) (4)	
Shellac, in ethanol, % w/w)	
Isopropyl alcohol[b] (% w/w)	
Black iron oxide[b] (% w/w)	
n-Butyl alcohol[b] (% w/w)	
Propylene glycol[b] (% w/w)	
Ammonium hydroxide %[b] (% w/w)	

(b) (4)

(b) (4)

(b) (4)

(b) (4)

As shown in the table above, the components of each of the (b) (4) used in the different strength oxycodone ARIR tablets are justified. It is noted that (b) (4) is not specifically listed in the FDA IID; however, each of the components are. Thus, there are no nonclinical safety concerns with (b) (4) in the proposed formulation.

Black Iron Oxide and Iron Oxide Yellow

It is noted that black iron oxide (b) (4) is not listed in the FDA IID; however, (b) (4) is. (b) (4) There is adequate coverage for the (b) (4) amounts of black iron oxide and the (b) (4) mg/day of iron oxide yellow at the MTDD of (b) (4) mg/day of oxycodone ((b) (4) tablets). Thus, there are no nonclinical safety concerns with black iron oxide and iron oxide yellow in the proposed formulation.

(b) (4)

(b) (4) Thus, the levels of (b) (4) in this proposed formulation ((b) (4) mg of the excipient at the MTDD of (b) (4) mg/day of oxycodone) are adequately justified for safety.

Xanthan Gum (CAS 11138-66-2)

Xanthan gum may be used safely in foods according to 21 CFR §172.695. There is no limitation listed in the CFR in terms of dose. An ADI (average daily intake) for xanthan

(b) (4)

gum was previously established by JECFA (Joint FAO/WHO Expert Committee on Food Additives) at up to 10 mg/kg, which is 600 mg for an average human weighing 60 kg; however, new data has been presented to further weigh in on the determination of the ADI[5]. New 2-year studies in rats failed to demonstrate carcinogenicity and toxicity attributed to xanthan gum, negative results in reproduction studies in rats, and no toxic effects in short-term studies in rats, rabbits, guinea pigs, and dogs as evaluated by JECFA. It is suggested by JECFA that up to 10-13 grams daily in humans indicated no adverse effects. Thus, the levels of xanthan gum in this proposed formation ((b) (4) mg of the excipient at the MTDD of (b) (4) mg/day of oxycodone) are adequately justified for safety.

(b) (4) The maximum daily level of (b) (4) in the proposed formulation at the MTDD of (b) (4) mg/day of oxycodone is (b) (4) mg. The level of (b) (4) in this proposed drug product is (b) (4) in the approved Morphabond™ (NDA 206544) at the MTDD of (b) (4) Thus, the levels of (b) (4) in this proposed formulation ((b) (4) mg of the excipient at the MTDD of (b) (4) mg/day of oxycodone) are adequately justified for safety.

(b) (4) (b) (4) is not specifically listed in the IID. The maximum daily level of (b) (4) in the proposed formulation at the MTDD of (b) (4) mg/day of oxycodone is (b) (4) mg. The level of (b) (4) in the proposed drug product is (b) (4) in the approved Morphabond™ (NDA 206544) at the MTDD of that product.

As described in the nonclinical reviews by this reviewer and Dr. Mellon (see nonclinical reviews dated September 2, 2015, September 14, 2015, and December 18, 2015 for Morphabond™ NDA), there were a number of PMRs for Morphabond™ that were issued to Inspirion for toxicology studies that were needed to fully qualify the (b) (4) was not in any FDA-approved products at the time the Morphabond™ application was under review. The reader is referred to these nonclinical reviews for a discussion on the safety of the (b) (4) used in Morphabond™. The currently outstanding PMR studies include a 6-month rodent and 9-month nonrodent general toxicology study with (b) (4) and a 2-year carcinogenicity assessment of (b) (4). Although not an

[5] JECFA is the Joint FAO/WHO Expert Committee on Food Additives. From the WHO Food Additives Series 21 online reference available at http://www.inchem.org/documents/jecfa/jecmono/v21je13.htm

approval issue for this NDA, the same PMRs for the qualification of (b) (4) should be issued for this NDA.

(b) (4)

(b) (4) is not specifically listed in the IID (although it used to be). Currently the IID only refers to the generic chemical term, (b) (4) which makes assessment of the specific (b) (4) products difficult. That being said, the maximum potency of (b) (4) in an FDA approved chronic oral drug product is (b) (4) mg. That product is dosed twice a day to result in a daily exposure to (b) (4) mg. Therefore, the use of this excipient is not novel and there are no nonclinical safety concerns with (b) (4) in the proposed formulation.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

Information on the drug substance, oxycodone hydrochloride, is supplied via reference to the data in MF (b) (4). The following table illustrates the proposed drug substance specifications that represent the Applicant's acceptance criteria (data from the Applicant's submission):

Table 3: Drug Substance Specifications

(b) (4)	Acceptance Criteria	Reviewer's Comments
	NMT (b) (4) %	Acceptable as per ICH Q3A(R2). See DMF Review for data on (b) (4).
	NMT (b) (4) %	Acceptable as per ICH Q3A(R2) and an approved drug

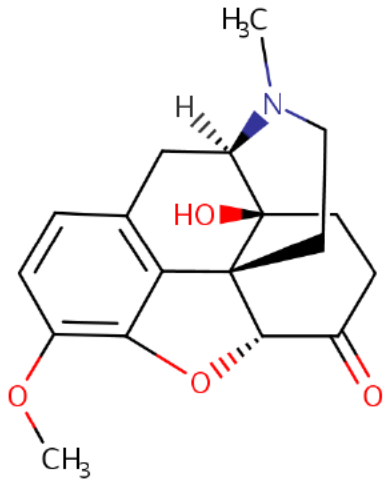
[redacted]		[redacted] (b) (4)	Acceptable as per ICH Q3A(R2)
			Acceptable as per ICH Q3A(R2)
			Acceptable as per ICH Q3A(R2)
			Acceptable as per ICH Q3A(R2)
			Acceptable as per ICH Q3A(R2) and an approved drug
Individual unspecified impurities		NMT (b) (4) %	Acceptable as per ICH Q3A(R2)
Total impurities		NMT (b) (4) %	Defer to CMC review team
Residual Solvents:			Acceptable (b) (4)

(b) (4)		NMT (b) (4) ppm	(b) (4)

The maximum daily dose of oxycodone is (b) (4) mg/day via this proposed product. For a drug product with a maximum daily dose of (b) (4) g/day, the ICH Q3A(R2) qualification thresholds are NMT (b) (4) % or (b) (4) mg per day intake (whichever is lower). The proposed drug substance specifications as shown in the table above meet ICH Q3A(R2) qualification thresholds. Moreover, MF (b) (4) has been used in a number of products with the same drug substance impurity profile (see MF (b) (4) quality review dated May 19, 2016). As such, there is clinical experience with these levels of the drug substance impurities.

It is important to note that (b) (4) , which is a structural alert for genotoxicity. The structure (b) (4) is illustrated below (from the Applicant's submission):

Figure 2: Structures of Oxycodone and (b) (4)

Oxycodone	(b) (4)
	

Adequate information exists to support the proposed specification for (b) (4) The reader is referred to the nonclinical review of DMF (b) (4) for further information.

Thus, the proposed drug substance specifications are acceptable.

Drug Product
The following table illustrates the proposed drug product specifications for all strengths (5, 15, and 30 mg) of the oxycodone ARIR tablets (data from the Applicant's submission):

Table 4: Drug Product Specifications

Degradant	Acceptance Criteria	Reviewer's Comments
(b) (4)	NMT (b) (4) %	Acceptable as per ICH Q3B(R2).
Single largest unknown impurity	NMT (b) (4) %	Acceptable as per ICH Q3B(R2).
Total impurities	NMT (b) (4) %	Defer to CMC review team.
(b) (4)	NMT (b) (4) ppm	Acceptable (b) (4)

The maximum daily dose of oxycodone is (b) (4) mg/day via this proposed product. For a drug product with a maximum daily dose of (b) (4), the ICH Q3B(R2) qualification thresholds are NMT (b) (4) mg TDI, whichever is lower. The proposed drug product specifications meet ICH Q3B(R2) qualification thresholds. Thus, the proposed drug product specifications are acceptable.

Container Closure System
As this drug product is formulated into tablets, a drug-specific assessment of the extractables and leachables from the container closure system will not be required as long as the container closure system is acceptable to the CMC review team via reference to indirect food additive regulations in 21 CFR §174-186.

2.6 Proposed Clinical Population and Dosing Regimen

The indications for RoxyBond™ are similar to Roxicodone®. The proposed indication for RoxyBond™ is for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. RoxyBond™ is proposed to be available as 5, 15, and 30 mg tablets. The proposed dosing regimen for initial dosing is 5 to 15 mg every 4 to 6 hours as needed for pain. For maintenance dosing, the lowest dose should be used to achieve pain relief. For opioid tolerant patients, the potency of the prior opioid relative to oxycodone should be factored into the selection of the total daily dose of oxycodone. The proposed labelling states that the safety and efficacy of oxycodone in pediatric patients have not been evaluated. As noted previously, due to the development of tolerance, there is no maximum daily dose of full agonist opioids. As such, the Division has employed a maximum theoretical daily dose (MTDD) for opioid tolerant individuals based on clinical use data and reasonable clinical practices. For an immediate release full agonist opioid dosed every 4-6 hours, the Division has established the MTDD as (b) (4) pills of the highest dosage form of the product. In this case, the MTDD for RoxyBond is (b) (4) pills/day x 30 mg/pill = (b) (4) mg/day.

2.7 Regulatory Background

The Applicant is submitting NDA 209777 via the 505(b)(2) regulatory pathway and is relying upon the Agency's previous findings of safety for Roxicodone® (NDA 21011) to support the proposed clinical study using their formulation of oxycodone hydrochloride ARIR oral tablets. The referenced drug product, oxycodone hydrochloride (Roxicodone®) was approved on August 31, 2000.

The nonclinical development program oxycodone hydrochloride ARIR was conducted under IND 105951 with Inspirion Delivery Technologies, LLC as the Sponsor. IND 105951 was originally submitted on November 29, 2013 and has been on active status as of December 29, 2013. In August 2016, the regulatory responsibility of oxycodone hydrochloride ARIR was transferred from Inspirion Delivery Technologies, LLC to Inspirion Delivery Sciences, LLC. Inspirion Delivery Sciences, LLC is the current Applicant of this NDA.

Inspirion Delivery Technologies, LLC also submitted the marketing application for Morphabond™ (NDA 206544) on November 21, 2014. The NDA was transferred to Daiichi Sankyo, Inc. on November 22, 2016. Inspirion Delivery Sciences, LLC has obtained a letter of authorization in SDN 7 from Daiichi Sankyo, Inc. allowing FDA to reference NDA 206544 for the purposes of justification of the safety of the tablet technology.

There was a preIND meeting with the Applicant prior to the IND submission under IND 105951 on February 16, 2010. Since that time, there have not been any further meetings with the Applicant regarding oxycodone hydrochloride ARIR.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study Number
(b) (4)	

(b) (4)

It is noted that (b) (4) was the former name for (b) (4). These studies were previously reviewed in the Morphabond™ application and the reader is referred to the nonclinical review for more details (see nonclinical review dated September 2, 2015 for NDA 206544).

3.2 Studies Not Reviewed

The studies outlined below were evaluated for relevance to the NDA submission but not formally reviewed because they were not deemed necessary for approval (see table below):

Study Title	Study Number
(b) (4)	

It is noted that (b) (4) was the former name for (b) (4)

3.3 Previous Reviews Referenced

The nonclinical review for Morphabond™ is referenced in this NDA (see nonclinical review dated September 2, 2015).

4 Pharmacology

4.1 Primary Pharmacology

There were no new primary pharmacology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

4.2 Secondary Pharmacology

There were no new secondary pharmacology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

4.3 Safety Pharmacology

There were no new safety pharmacology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no new nonclinical pharmacokinetics or ADME studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

5.2 Toxicokinetics

There were no toxicokinetics studies with oxycodone submitted in this NDA or required for this 505(b)(2) application.

6 General Toxicology

There were no general toxicology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

7 Genetic Toxicology

There were no genetic toxicology studies with oxycodone hydrochloride submitted in this NDA or required for this 505 (b)(2) application.

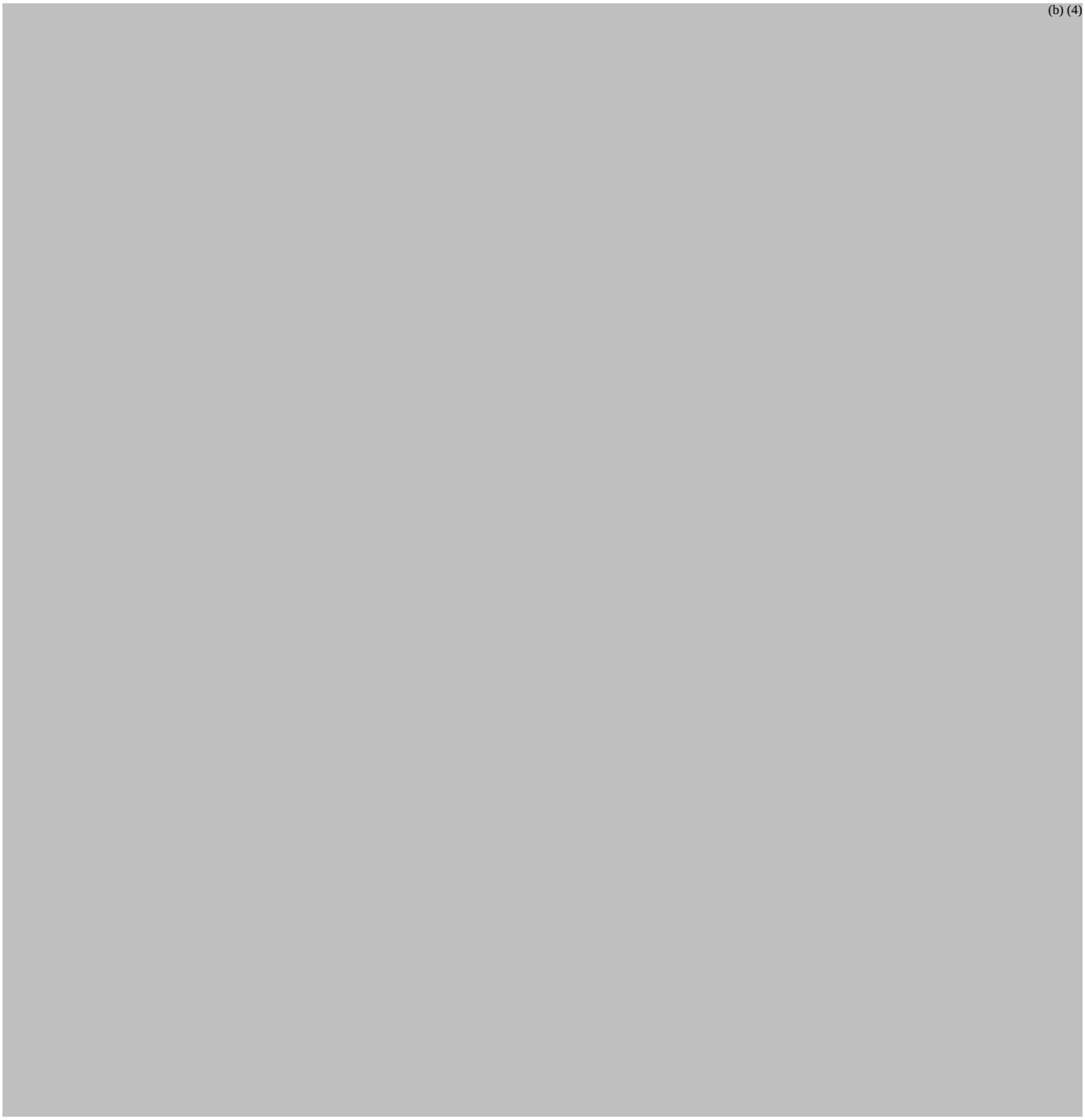
8 Carcinogenicity

There were no carcinogenicity studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

(b) (4)



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Thus, the fertility statements proposed by the Applicant for inclusion in Sections 8.1, 8.3, and 13.1 of the label are not appropriate.

10 Special Toxicology Studies

There were no special toxicology studies with oxycodone hydrochloride submitted in this NDA or required for this 505(b)(2) application.

11 Integrated Summary and Safety Evaluation

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 and drug product specifications as well as 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 with 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, PMRs issued for Morphabond™ to conduct toxicology studies in order to qualify the safety of the (b) (4) should be issued 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). From a nonclinical pharmacology toxicology perspective, the proposed drug product, oxycodone hydrochloride ARIR, may be approved.

12 Appendix/Attachments

References

Davis CP, Franklin LM, Johnson GS, and Schrott LM. 2010. Prenatal Oxycodone Exposure Impairs Spatial Learning and/or Memory in Rats. *Behav Brain Res.* **212**:27-34.

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/s/

CARLIC K HUYNH
03/31/2017

RICHARD D MELLON
03/31/2017
I concur.

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	105951
Supporting document/s:	SDN 4
Sponsor's letter date:	November 26, 2013
CDER stamp date:	November 29, 2013
Product:	Oxycodone HCl ARIR (abuse-resistant, immediate-release) tablets
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate
Sponsor:	Inspirion Delivery Technologies, LLC
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Carlic K. Huynh, PhD
Supervisor/Team Leader:	R. Daniel Mellon, PhD
Division Director:	Bob A. Rappaport, MD
Project Manager:	Swati Patwardhan

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Sponsor, Inspirion Delivery Technologies, is developing an abuse-resistant immediate-release (ARIR) tablet formulation for oxycodone hydrochloride for the management of moderate to severe pain. The Sponsor is proposing a 505(b)(2) NDA submission referencing Roxicodone® (NDA 21011) for the Agency's previous findings of safety for oxycodone.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical studies submitted in this IND to support the proposed clinical protocol. There were no nonclinical safety concerns with the drug product and drug substance specifications. Although the formulation contains excipients that are not found in the FDA Inactive Ingredients Database (IID), the levels of these excipients are supportive of the proposed clinical protocol via a combination of the maximum amounts found in the FDA IID, toxicology studies in DMFs (b) (4) and (b) (4) and the conclusions made by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The maximum daily dose for this drug product was not established at the time of IND submission; however, based upon review of the clinical use data submitted as well as data from similar development programs, the Division (on 1/7/2014) has decided that for IR opioids dosed every 4-6 hours, the maximum daily dose will be based on (b) (4) pills per day. (b) (4) (b) (4) Although the Sponsor submitted an Excipient Safety Report, the report was based on an MDD of (b) (4) mg/day oxycodone and did not address all excipients. A revised report will have to be requested. The adequacy of the final Excipient Safety Assessment Report to support the NDA will be addressed in the review of the NDA submission. Additional information for the (b) (4) excipient including the safety justification of (b) (4) up to the MTDD of IR oxycodone will be required for the NDA submission.

One of the protocols in the proposed clinical protocols of this IND involves the intranasal administration of the crushed 30 mg oxycodone ARIR tablet (Protocol O-ARIR-002). As per Division policy, the patient population includes experienced drug users, specifically those with experience crushing and snorting opioid pills and an informed consent that adequately addresses the risks of crushing and snorting tablets.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

From a nonclinical pharmacology toxicology perspective, the proposed clinical protocol in this IND is allowed to proceed at the discretion of the Medical Officer.

1.3.2 If Not Safe to Proceed

Nonclinical deficiencies

Nonclinical information needed to resolve deficiencies

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

The Sponsor has included the following question to the Agency:

Does the Division agree that the Excipient Safety Assessment Report is sufficient to demonstrate the safety of the excipients used in IDT's Oxycodone ARIR tablets to fulfill NDA safety registration requirements?

FDA Response: Upon preliminary review of the Excipient Safety Assessment Report provided, we cannot agree that you have provided adequate justification for the safety of the excipients via this drug product formulation. First, based upon review of clinical use data from additional sources, the Division has determined that the maximum theoretical daily dose (MTDD) for this immediate-release opioid drug product, dosed every 4-6 hours, will be (b) (4) mg/day or (b) (4) pills per day. Revise the Excipient Safety Assessment Report to reflect this MTDD. Second, the report does not provide safety justification for the apparent novel excipient (b) (4). As this excipient is not listed in the CDER Inactive Ingredients Database, it is deemed novel and must be adequately justified for safety.

We have not yet completed a full review of all of the studies in the referenced master files to determine their adequacy to support an NDA. Final determination of the adequacy of the formulation can only be provided upon review of the entire NDA submission.

Submit copies of all cited references in the revised Excipient Safety Assessment Report.

2 Drug Information

2.1 Drug

CAS Registry Number
124-90-3

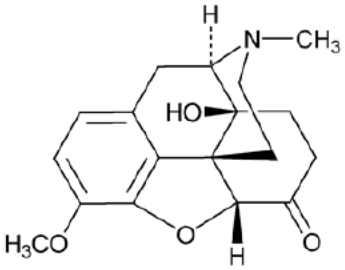
Generic Name
Oxycodone hydrochloride

Code Name NONE

Chemical Name
(5α)-4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride (9CI)

Molecular Formula/Molecular Weight
$C_{18}H_{21}NO_4$•HCl / 351.82 g/mol

Structure or Biochemical Description



• HCl

Pharmacologic Class
Opioid agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
21011	Roxicodone®	DAAAP	5, 15, and 30 mg (oral)	AP	August 31, 2000	Management of moderate to severe pain where use of an opioid analgesic is appropriate	Mallinckrodt, Inc.

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
		(b) (4)	February 23, 2010	Specifications for (b) (4) are both NMT (b) (4) %, which are as low as technically feasible
			February 8, 1977	The toxicology studies conducted appear to use (b) (4) There is no review in DARRTs of these toxicology studies
			September 7, 2007	Approved in numerous ANDAs to other drug products

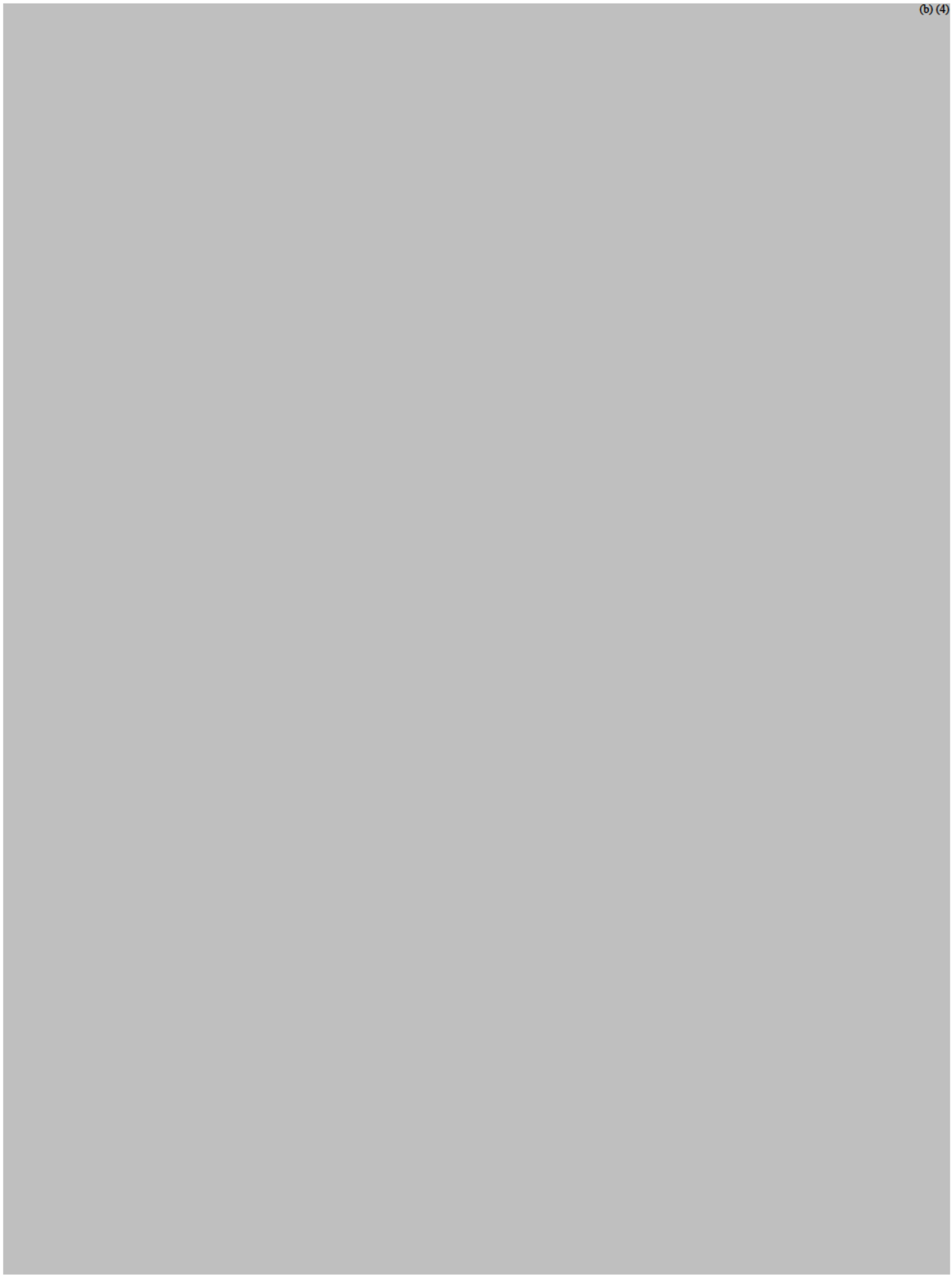
2.3 Drug Formulation

The proposed drug product is a smooth surface tablet that the Sponsor expects to pass through the gastrointestinal tract intact (b) (4) . The image below was reproduced from the submission:

(b) (4)

The following table illustrates the drug product formulation (b) (4) (adapted from the Sponsor's submission):

(b) (4)


(b) (4)

(b) (4)

The following table illustrates the levels of each excipient compared to the FDA Inactive Ingredients Database (IID) and when the total dose in this IND is considered as well as the maximum number of tablets for the NDA. The MTDD for IR oxycodone drug products is not clear and depends on the dose of the drug product. Historically, for other IR oxycodone drug products of lower dose forms (5-7.5 mg tablets), and the Division's approach was to determine the MTDD based on clinical use data. Based on data for these lower strength products, the MTDD of immediate release oxycodone ranged from 80 to 200 mg/day. A MTDD for a 30 mg IR oxycodone drug product has not been determined and clinical use data was required from this Sponsor at the time of the preIND. In this submission, the Sponsor proposes a MTDD for oxycodone at (b) (4) mg/day. This would be approximately (b) (4) tablets via the 30 mg oxycodone ARIR tablets. Based upon review of the clinical use data submitted as well as data from similar development programs, the Division (on 1/7/2014) has decided that for IR opioids dosed every 4-6 hours, the maximum daily dose will be based on (b) (4) pills per day. (b) (4)

(b) (4)

There are (b) (4) drug product formulation and the table below lists the total amount of the excipients (b) (4).

(b) (4)

(b) (4)

(b) (4)

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2.4 Comments on Novel Excipients

All excipients were found in the FDA IID at some level with the exception of (b) (4)

(b) (4)

(b) (4)

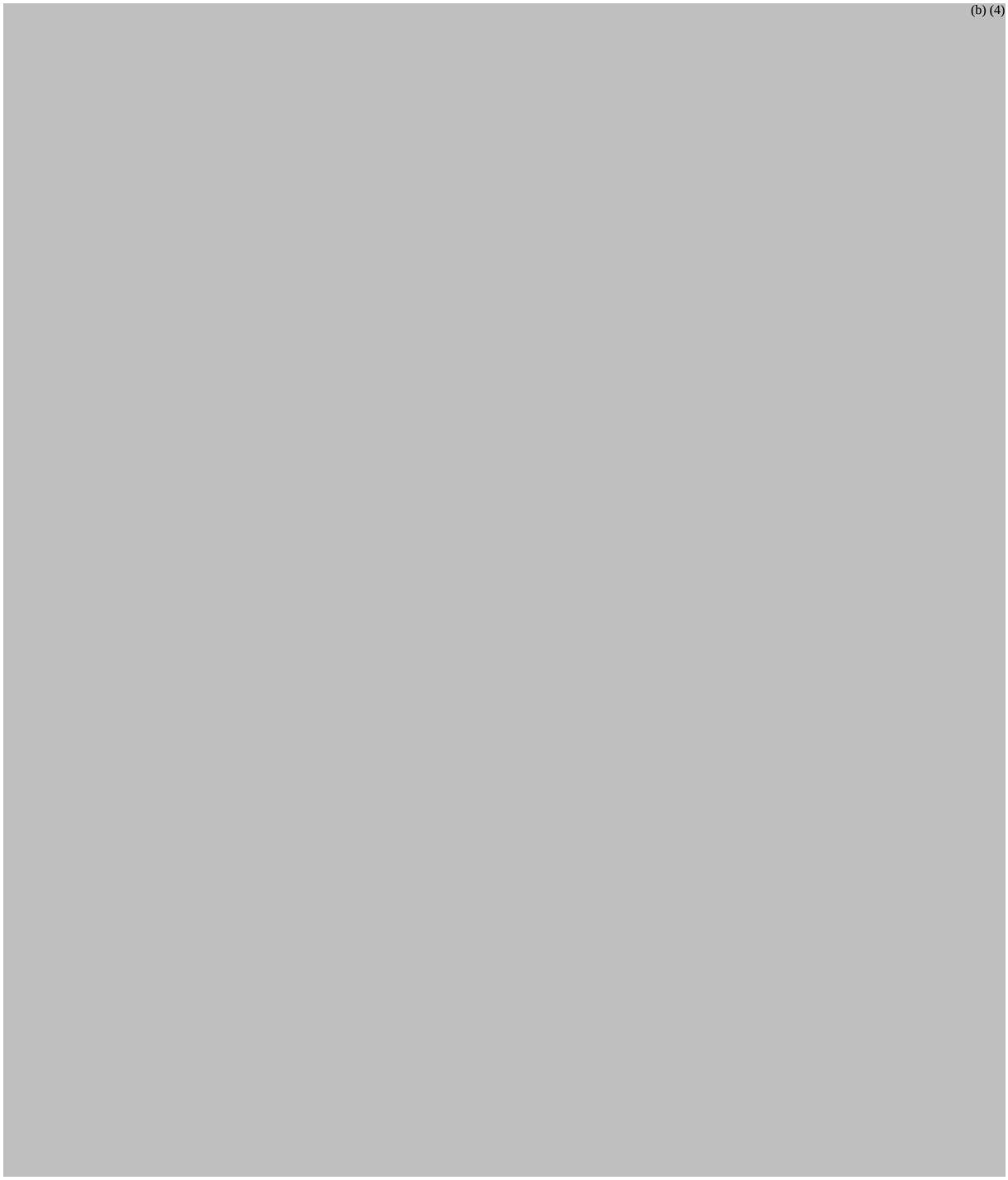
, which is listed in the IID with a maximum potency of (b) (4) mg per dosage form and is therefore not a novel use of this excipient for the proposed clinical protocol. In addition, toxicology studies have apparently been completed with (b) (4) and are included in the referenced MF (b) (4)

As per the IND, the MF contains the following studies:

7. APPENDIX I

STUDIES PEFORMED BY (b) (4)

(b) (4)


(b) (4)

(b) (4)

These toxicology studies were not reviewed formally for the purposes of the initial IND, as the use of the compound is not novel for the single-dose study. These studies will be reviewed for the NDA.

The IND also contains a toxicological risk assessment for (b) (4) as prepared by (b) (4) The risk assessment summarizes studies conducted in the early 1970s and a scientific opinion by the European Food Safety Assessment (EFSA) Panel on Food Additives and Nutrient Sources. As per the table above, most of the toxicology studies are also found in the MF and were all completed prior to GLPs, which were required beginning in 1979. They appear to lack full line listings and formal review will be required for the NDA.

Based on the listing above, there does not appear to be a chronic toxicology study in the non-rodent model, fertility and early embryonic development studies, a pre- and post-natal development study or a carcinogenicity assessment. The Sponsor is presumably intending to leverage the data for (b) (4) for a 6-month nonrodent toxicology study. The adequacy of this study will depend on the findings and justification that (b) (4) is adequately comparable to (b) (4).

(b) (4)
.
(b) (4) is not listed in the IID. Thus, (b) (4) is considered a novel excipient.

(b) (4)

(b) (4)

Polyethylene glycol (b) (4)

(b) (4)

This (b) (4) has been used in numerous topical drug products, including soaps and shampoos . (b) (4) The MF will be reviewed separately.

Polyethylene glycol (b) (4) which is present in approved topical products. Polyethylene glyco (b) (4) is present in an oral product (b) (4) however, the amount of this excipient in the drug product cannot be verified at this time. The Sponsor states that (b) (4) contain polyethylene glyco (b) (4); however, the exact amount of polyethylene glycol (b) (4) is not provided and we have not been able to verify either the presence of or the amount present in these products.

(b) (4)

As of the date of this review, although we are not concerned with the safety of the backbone in (b) (4) we have been unable to provide definitive safety justification for the proposed levels of the (b) (4) this novel excipient. We note that we are not concerned with the safety of the backbone in (b) (4) and the

[1] http://whatsinproducts.com/chemicals/view/1/836

(b) (4) Therefore, the levels of (b) (4) that would be present due to the proposed clinical protocol do not represent a safety concern.

(b) (4) is not specifically listed in the FDA IID. Thus, (b) (4) is a novel excipient.

(b) (4) These data suggest a lack of concern for the proposed clinical study; however, the Sponsor should still be requested to provide a more definitive discussion of the safety of this excipient for the NDA.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4). Collectively, the levels of (b) (4) in the oxycodone ARIR formulation would not represent a safety concern in the proposed clinical protocol.

Xanthan Gum (CAS 11138-66-2).
Xanthan gum may be used safely in foods according to 21 CFR §172.695. Moreover, an ADI (acceptable daily intake) for xanthan gum was previously established by JECFA (Joint FAO/WHO Expert Committee on Food Additives) at up to 10 mg/kg, which is 600 mg for an average human weighing 60 kg; however, new data has been presented to further weigh in on the determination of the ADI[5]. New 2-year studies in rats failed to demonstrate carcinogenicity and toxicity attributed to xanthan gum, negative results in reproduction studies in rats, and no toxic effects in short-term studies in rats, rabbits, guinea pigs, and dogs as evaluated by JECFA. It is suggested by JECFA that up to 10-13 grams daily in humans indicated no adverse effects. Thus, the levels of xanthan gum in the proposed clinical protocol via the oxycodone ARIR formulation do not represent a safety concern.

Sponsor's Excipient Safety Assessment Report.
The Sponsor submitted an excipient safety assessment report for the levels of some of the excipients when considering their proposed maximum theoretical daily dose (MTDD) of (b) (4) mg of IR oxycodone. The excipients included in the excipient safety assessment report were (b) (4), xanthan gum, colloidal silicon dioxide, (b) (4) and polyvinyl alcohol.

Reviewer's assessment:
The safety of (b) (4) for the NDA may be justified by the toxicology studies contained in DMF (b) (4). Given the experience with the (b) (4) drug class and based on the information provided to date, there are no clear safety concerns in terms of this IND. The adequacy of the information to support an NDA at the MTDD has not been fully addressed at this time. In general, the adequacy of these studies will be addressed during review of the NDA submission. The safety of (b) (4) and xanthan gum has been addressed above. The safety of colloidal silicon dioxide and polyvinyl alcohol has been addressed above. The levels of the excipients colloidal silicon dioxide and polyvinyl alcohol have been qualified in approved products found via the FDA IID. Although the proposed clinical study in this IND submission may proceed, it is not yet clear that the information contained in the Excipient Safety Assessment Report is adequate for filing the NDA submission and the

[4] Evaluation of certain food additives and contaminants. Thirty-fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 789. 1990.

[5] http://www.inchem.org/documents/jecfa/jecmono/v21je13.htm

report should be revised to address the MTDD of (b) (4) mg/day ((b) (4) pills) and include (b) (4).

In addition, the Sponsor should submit all published literature references cited in the excipient safety assessment report.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

Information regarding the drug substance, oxycodone HCl, is referenced in DMF (b) (4) The following tables illustrate the drug substance specifications (adapted the Sponsor's submission):

Table 2.3.S.4-1 API Manufacturer's Test (b) (4) Specifications for API			
HPLC Impurities: (b) (4)	Not more than (b) (4) ppm (calculated on the (b) (4)	USP Monograph	USP
HPLC Impurities: (b) (4)	Not more than (b) (4) % Not more than % Not more than % Not more than % Not more than % Not more than %	USP Monograph	USP
Single greatest unknown	Not more than %		
Total Impurities	Not more than %		
Residual solvents: (b) (4)	Not more than (b) (4) ppm	USP <281>	USP

Table 3.2.S.4-2 Drug Product Manufacturer's [redacted] Test Specifications for API			
Test	**Specification**	**Method**	**Quality Standard**
[redacted]			
	NMT [redacted] ppm	USP [redacted]	USP [redacted]
	NMT [redacted] ppm		
Limit of [redacted]	NMT [redacted] %	USP Monograph	USP
Limit of [redacted]	NMT [redacted] %	USP Monograph	USP
Impurities [redacted]			
Limit of [redacted]	NMT [redacted] %	USP Monograph	USP
Impurities [redacted]			
[redacted]	NMT [redacted] %	USP Monograph	USP
	NMT [redacted] %		
	NMT [redacted] %		
	NMT [redacted] %		
	NMT [redacted] %		
	NMT [redacted] %		
Individual unspecified impurity	NMT [redacted] %		

As shown in the tables above, the specifications meet ICH Q3A(R2) qualification threshold of NMT [redacted]% or [redacted] mg per day intake (whichever is lower) for drug products with a maximum daily dose of [redacted] g/day of oxycodone. Moreover, the specifications of [redacted] are NMT [redacted]%, each, which are as low as technically feasible.

The Sponsor submitted the batch analysis of oxycodone HCl, Lot Number 1036X008, which was performed at 2 different laboratories.

The following table illustrates the batch analysis of oxycodone HCl, Lot Number 1036X008 as performed by [redacted] (adapted from the Sponsor's submission):

Test	Specification	Result
(b) (4) Content	(b) (4) % (Calculated on the (b) (4)	(b) (4) %
Description	White to off-white crystals or powder	Conforms
HPLC Assay	(b) (4) % (Calculated on the (b) (4)	(b) (4) %
HPLC Impurities- (b) (4)	Not more than (b) (4) %	(b) (4) %
HPLC Impurities- (b) (4)	Not more than (b) (4) ppm (Calculated on the (b) (4) (b) (4)	(b) (4) ppm
HPLC Impurities- (b) (4)	Not more than (b) (4) %	(b) (4) %
HPLC Impurities- (b) (4)	Not more than %	%
HPLC Impurities- (b) (4)	Not more than %	%
HPLC Impurities-	Not more than %	%
HPLC Impurities-	Not more than %	%
HPLC Impurities- Single Greatest Unknown Impurity	Not more than %	%
HPLC Impurities- Total Impurities	Not more than %	(b) (4) %
Residual Solvents- (b) (4)	Not more than (b) (4) ppm	ppm

As shown in the table above, the results of the batch analysis show that the levels of the residual solvents and impurities are lower than the specifications.

The following table illustrates the batch analysis of oxycodone HCl, Lot Number 1036X008 as performed by (b) (4) (adapted from the Sponsor's submission):

TESTS	RESULTS	SPECIFICATIONS	METHOD
Oxycodone Related Compound (b) (4)	(b) (4) %	NMT (b) (4) %	USP 35 / NF 30
Oxycodone Related Compound (b) (4)	None Detected	NMT %	USP 35 / NF 30
(b) (4)	(b) (4) %	(b) (4) %	USP 35 / NF 30
Optical Rotation:	-145°	-137° to -149°	USP 35 / NF 30
(b) (4)			
Residual Solvents:			USP 35 / NF 30
(b) (4)	(b) (4) ppm	NMT (b) (4) ppm	
	None Detected	NMT ppm	
	(b) (4) ppm	NMT ppm	
Impurity, (b) (4)			USP 35 / NF 30
(b) (4)	None Detected	NMT (b) (4) %	
	None Detected	NMT %	
	None Detected	NMT %	
	None Detected	NMT %	
	None Detected	NMT %	
	None Detected	NMT %	
Individual Unspecified Impurity:	(b) (4) %	NMT %	
Total:	%	NMT %	

As shown in the table above, the results of the batch analysis show that the levels of the residual solvents and impurities are either not detected or lower than the specifications.

The following table illustrates the residual solvents in the drug substance (from the Sponsor's submission):

Table 2.3.S.3-2 Residual Solvents

Impurity	Molecular Formula	Specifications	Results
(b) (4)		NMT (b) (4) ppm	(b) (4) ppm
		NMT ppm	ND
		NMT ppm	(b) (4) ppm

As shown in the table above, (b) (4) residual solvent with a limit of NMT (b) (4) ppm as per ICH Q3C, (b) (4) or (b) (4) is a (b) (4) residual solvent with a limit of (b) (4) ppm as per ICH Q3C, and (b) (4) is a Class 2 residual solvent with a limit of NMT (b) (4) ppm as per ICH Q3C. The specifications and results for these residual solvents meet ICH Q3C limits.

At this time of development, there are no safety concerns with the drug substance specifications and the residual solvents. However, the specifications of the drug

substance impurities must comply with ICH Q3A(R2) qualification thresholds for the NDA submission.

Drug Product

The following table illustrates the drug product specifications (adapted from the Sponsor's submission):

Table 3.2.P.5.1-1 Finished Product Specifications for Oxycodone Hydrochloride ARIR Tablets, 30 mg 15mg and 5mg

Test	Specification	Method
Related Substances		
(b) (4)	NMT (b) (4) % (w/w)	
	NMT (b) (4) % (w/w)	
Single largest impurity	NMT % (w/w)	
Total impurities	NMT % (w/w)	
(b) (4)	(b) (4) NMT (b) (4) ppm	USP 35/NF 30

*For information purpose only

As shown in the table above, the specifications meet ICH Q3B(R2) qualification threshold of NMT (b) (4) % or (b) (4) mcg per day (whichever is lower) for drug products with a maximum daily dose of 10 to 100 mg. (b) (4) and (b) (4) do not contain structural alerts for genotoxicity and thus can be regulated as non-genotoxic drug product degradants. Regardin (b) (4) which the specification meets.

The Sponsor has submitted the batch analysis of several batches of oxycodone HCl ARIR tablets, 30 mg. These batches are C005012, C006613, and C006913.

The following table illustrates the batch analysis done on batch number C005012 (adapted from the Sponsor's submission):

Tests	Specifications	Results
Related Substances:		
a) (b) (4)	a) NMT (b) (4) %	a) (b) (4) %
b)	b) NMT %	b) %
c) Single largest Impurity	c) NMT %	c) %
d) Total Impurities	d) NMT %	d) %

Tests	Results	Specifications	Date Tested
		(b) (4)	1/4/2013

As shown in the table above, the results of the batch analysis show that the levels of the (b) (4) degradants was below the specifications.

The following table illustrates the batch analysis done on Batch Number C006613 (adapted from the Sponsor's submission):

Tests	Specifications	Results
Related Substances:		
a) (b) (4)	a) NMT (b) (4)%	a) 0. (b) (4) %
b)	b) NMT 5%	b) 0. %
c) Single largest Impurity	c) NMT %	c) 0. %
d) Total Impurities	d) NMT %	d) 0. %
***Related Substances:**		
a) (b) (4)	a) Ma (b) (4) ppm	a) (b) (4) ppm

As shown in the table above, the results of the batch analysis show that the levels of the (b) (4) degradants are below the specifications.

The following table illustrates the batch analysis done on Batch number C006913 (adapted from the Sponsor's submission):

Tests	Specifications	Results
Related Substances: (b) (4)		
a)	a) NMT (b) (4) %	a) (b) (4) %
b)	b) NMT %	b) %
c) Single largest Impurity	c) NMT %	c) %
d) Total Impurities	d) NMT %	d) %
***Related Substances:**		
a) (b) (4)	a) Max (b) (4) ppm	a) (b) (4) ppm

As shown in the table above, the results of the batch analysis show that the levels of the (b) (4) degradants are below the specifications.

At this time of development, there are no safety concerns with the drug product specifications. However, the specifications of the drug product degradants must comply with ICH Q3B(R2) qualification thresholds for the NDA submission.

2.6 Proposed Clinical Protocol

The Sponsor has included protocols for 2 clinical studies. Protocol O-ARIR-002 is an intranasal "likeability" study and Protocol O-ARIR-003 is a bioavailability study.

Protocol O-ARIR-002 is entitled "A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Four-Way Crossover Study to Assess the Relative Bioavailability and Abuse Potential of Intranasal Administration of Ground Oxycodone ARIR Tablets (Abuse Deterrent) versus an Equivalent Dose of Crushed Roxicodone® in Nondependent Recreational Opioid Users." The patient population is experienced opioid users who are not currently physically dependent on opioids including patients that have experience with intranasal drug administration. The patient population includes both males and females of 18 to 55 years of age and the inclusion criteria include the use of at least 1 method of contraception per sex. Each participant will be

subjected to the following 4 treatments with a minimum 72-hour washout period between treatments (from the Sponsor's submission):

Tx	Tampered Intranasal Dose (Weight≈mg)	Intact Oral Dose
A	Ground placebo matching Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
B	Crushed 30 mg Roxicodone tablet (low volume, 100 mg)	Placebo tablet matching Oxycodone ARIR
C	Ground 30 mg Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
D	Placebo powder (microcrystalline cellulose) matching Roxicodone (low volume, 100 mg)	Intact 30 mg Oxycodone ARIR

Tx = Treatment

As shown in the table above, the participant will be subjected to two 30 mg oxycodone ARIR tablets (one crushed and one whole) in the proposed clinical protocol. The informed consent adequately addresses the risks of crushing and snorting tablets with the following wording (from the Sponsor's submission):

Snorting Risks

Snorting crushed pills can cause nasal pain or irritation, nasal blockage, and nasal drainage. The risks associated with snorting crushed pills containing oxycodone or any other drug are not well known; it has never been prescribed to anyone this way except in research studies. Oxycodone is snorted illegally by some people, but the safety is not known. The risks of snorting the oxycodone combined with the other additives (added ingredients) that are being studied are not known because it has not been well tested for safety. These additives may cause a lot of irritation inside your nose, including pain, burning, itching, runny nose, stuffiness, and other side effects which are not known. Side effects from snorting drugs and additives that have not been tested this way could also include damage to you nasal tissues, a loss of your sense of smell or damage to your lungs, including granulomas (a small area of inflammation in tissue due to injury).

Protocol O-ARIR-003 is entitled "A 3-Way Crossover Relative Bioavailability Study of Oxycodone ARIR (Abuse Resistant Immediate Release) 30 mg Tablets in Fasted State Versus Roxicodone® 30 mg Tablets in Fasted State Versus Oxycodone ARIR 30 mg Tablets in Fed State." The patient population is healthy subjects (male and females) aged 18-45 years. The subjects must be on at least one method of contraception per sex. Each subject will be treated to the following dosing regimen with at least 4 days washout between treatments (from the Sponsor's submission):

- 1 x 30 mg tablet of **test product (A)** given as a single dose with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours
- 1 x 30 mg tablet of **test product (A)** given as a single dose with approximately 240 mL (8 fluid ounces) of room temperature water in a fed state
- 1 x 30 mg tablet of **reference product (B)** given as a single dose with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours

As shown in the table above, each subject will be given two 30 mg oxycodone ARIR tablets in the proposed clinical protocol.

2.7 Previous Clinical Experience

There is extensive clinical experience with oxycodone. This will be the first clinical study for this drug product formulation.

2.8 Regulatory Background

There was a preIND meeting with the Sponsor in 2010 (the Sponsor was (b) (4) at that time). From the meeting minutes, the following nonclinical pharmacology toxicology comments were communicated with the Sponsor (see Meeting Minutes dated February 16, 2010):

> ***Pharm/Tox:***
> *All of the excipients included in (b) (4) formulation for the proposed ARIR Oxycodone product are listed in the FDA's Inactive Ingredient Guide (IIG) and are within the limits established for an oral extended-release tablet.*
> *In light of the above, (b) (4) does not intend to perform any additional toxicity studies to support its 505(b)(2) filing.*
>
> ***Question 3**: Does the FDA concur that no additional toxicology studies are needed for approvals?*
>
> **FDA Response:**
>
> 1. **Any novel excipients must be adequately qualified for safety. Safety justification for excipients must be submitted to the IND in accordance with the following guidance document: Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.**
> **As noted in the document cited above, "the phrase new excipients means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug**

substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration."

As an example (b) (4) **is not listed in the Inactive Ingredient Guide (IIG) in FDA approved drugs. Therefore this excipient should be qualified or justified for safety.**

2. **The maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the ICH guideline qualification thresholds for the acceptable levels of total amounts of excipients as well as impurity and degradant levels. You need to research prescribing patterns to determine the maximum theoretical dose for your IR product. That theoretical dose limit would be the basis for conducting safety toxicology assessments for the excipients used in the drug product.**

Additional Nonclinical Comments:

1. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Similar concern about the maximum daily dose as described previously will determine allowable specifications.**

   Adequate qualification must include:

   i. **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

   ii. **Repeat dose toxicology of appropriate duration to support the proposed indication (90 days for a chronic indication).**

   Genotoxic impurities or degradation products pose an additional risk; therefore, a specification of NMT 1.5 mcg/day must be set for genotoxic or potentially genotoxic residual intermediates or identified degradants unless qualified for safety. Adequate safety qualification for any potential genotoxic impurities must be provided with the NDA submission and must include:

   i. **Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

ii. **Should this qualification produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model**

iii. **Note that phenanthrene-derivative opioid drug products, such as oxycodone containing products, may contain impurities containing an α,β-unsaturated ketone moiety, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to NMT 1.5 mcg/day or adequate safety qualification must be provided as described above. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and, if needed, to decrease the limit of these impurities.**

2. **We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf)).**

   If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

DISCUSSION: No discussion necessary.

3 Studies Submitted

3.1 Studies Reviewed

There were no nonclinical studies with oxycodone submitted in this IND.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

There were no previous reviews referenced. (b) (4)

4 Pharmacology

4.1 Primary Pharmacology

There were no primary pharmacology studies with oxycodone submitted in this IND.

4.2 Secondary Pharmacology

There were no secondary pharmacology studies with oxycodone submitted in this IND.

4.3 Safety Pharmacology

There were no safety pharmacology studies with oxycodone submitted in this IND.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

There were no PK/ADME studies with oxycodone submitted in this IND.

5.2 Toxicokinetics

There were no toxicokinetic studies with oxycodone submitted in this IND.

6 General Toxicology

There were no general toxicology studies with oxycodone submitted in this IND.

7 Genetic Toxicology

There were no genetic toxicology studies with oxycodone submitted in this IND.

8 Carcinogenicity

There were no carcinogenicity studies with oxycodone submitted in this IND.

9 Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies with oxycodone submitted in this IND.

10 Special Toxicology Studies

There were no special toxicology studies with oxycodone submitted in this IND.

11 Integrated Summary and Safety Evaluation

There were no nonclinical studies submitted in this IND to support the proposed clinical protocol. There were no nonclinical safety concerns with the drug product and drug substance specifications. Although the formulation contains excipients that are not found in the FDA Inactive Ingredients Database (IID), the levels of these excipients are supportive of the proposed clinical protocol via a combination of the maximum amounts found in the FDA IID, toxicology studies in DMFs (b) (4) and (b) (4) the conclusions made by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and familiarity with the similar polymeric materials in the (b) (4) excipients. The MTDD proposed by the Sponsor is not acceptable and the safety assessment for the excipients will have to take into consideration the MTDD of (b) (4) mg (b) (4) tablets). The safety assessment should be revised accordingly and all excipients should be included in the justification. The adequacy of a revised Excipient Safety Assessment Report will be addressed in the review of the NDA submission (earlier if time and workload permit). Additional information for the (b) (4) excipient including the safety justification of (b) (4) up to the MTDD of IR oxycodone will be required for the NDA submission.

One of the protocols in the proposed clinical protocols of this IND involves the intranasal administration of the crushed 30 mg oxycodone ARIR tablet (Protocol O-ARIR-002). As per Division policy, the patient population includes drug users with experience in intranasal drug administration of crushed opioid pills and the informed consent adequately addresses the risks of crushing and snorting tablets.

Thus, from a nonclinical pharmacology toxicology perspective, the proposed clinical protocol in this IND is allowed to proceed at the discretion of the Medical Officer.

The Sponsor has included the following question to the Agency:

> *Does the Division agree that the Excipient Safety Assessment Report is sufficient to demonstrate the safety of the excipients used in IDT's Oxycodone ARIR tablets to fulfill NDA safety registration requirements?*

FDA Response: Upon preliminary review of the Excipient Safety Assessment Report provided, we cannot agree that you have provided adequate justification for the safety of the excipients via this drug product formulation. First, based upon review of clinical use data from additional sources, the Division has determined that the maximum theoretical daily dose (MTDD) for this immediate-release opioid drug product, dosed every 4-6 hours, will be (b) (4) mg/day or (b) (4) pills per day. Revise the Excipient Safety Assessment Report to reflect this MTDD. Second, the report does not provide safety justification for the apparent novel excipient (b) (4). As this excipient is not listed in the CDER Inactive Ingredients Database, it is deemed novel and must be adequately justified for safety.

We have not yet completed a full review of all of the studies in the referenced master files to determine their adequacy to support an NDA. Final determination of the adequacy of the formulation can only be provided upon review of the entire NDA submission.

Submit copies of all cited references in the revised Excipient Safety Assessment Report.

12 Appendix/Attachments

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

/s/

CARLIC K HUYNH
01/08/2014

RICHARD D MELLON
01/08/2014