CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209777Orig1s000

CHEMISTRY REVIEW(S)

FACILITIES

Product Background: First Review

The drug product is an abuse-resistant immediate-release (ARIR) formulation of oxycodone hydrochloride. The oral tablets will be manufactured in strengths of 5mg, 15mg, and 30mg. (b) (4) (b) (4) (b) (4) The product is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

NDA: 209777

Drug Product Name / Strength: Oxycodone hydrochloride ARIR Tablets (RoxyBond®), 5mg, 15mg, 30mg

Route of Administration: Oral

Applicant Name: Inspirion Delivery Sciences, LLC

Review Summary:

Based on review of the application and inspection histories for the associated facilities, the manufacturing facilities for NDA 209777 are found **acceptable**.

List Submissions being reviewed:

Reviewed Submissions		
Description	**SD # (Sequence)**	**Date**
Original Submission	1 (0001)	21-OCT-2016
Quality/Response to Information Request	10 (0010)	03-FEB-2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

There is a post-marketing commitment to update the stratified (b) (4) testing. The updated protocol requested in the PMC will be submitted following approval.

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Daniel DeCiero

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BIOPHARMACEUTICS

Product Background:

NDA: 209777

Drug Product Name / Strength: RoxyBond (Oxycodone ARIR) (Oxycodone hydrochloride) Immediate Release Tablets/5, 15, and 30 mg

Route of Administration: Oral

Applicant Name: Inspirion Delivery Sciences, LLC

Submission:

Inspirion Delivery Sciences, LLC (IDT) submitted NDA 209777, RoxyBond (Oxycodone ARIR tablet 5, 15 and 30 mg) under section 505(b)(2) using ROXICODONE® (NDA 021011;Mallinckrodt, Inc.) as the reference drug. RoxyBond (Oxycodone ARIR) is an abuse-deterrent, immediate release (IR) formulation for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The drug substance in Oxycodone ARIR is oxycodone hydrochloride. The clinical and nonclinical pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of oxycodone hydrochloride have been extensively characterized. IDT has not conducted any clinical efficacy studies of Oxycodone ARIR and is relying on FDA's previous findings of safety and efficacy of ROXICODONE. IDT has conducted comparative bioavailability (BA) and dose proportionality studies to bridge to FDA's finding of safety and efficacy for ROXICODONE.

Abuse deterrent formulation background

Normally, abusers crush the tablet into a powder and subsequently dissolve in water; then inject the liquid containing an immediately available dose of oxycodone or alternatively insufflating the powder intranasally to achieve a "high". Abuse of ROXICODONE in this manner poses a risk of overdose and death; this risk is increased with concurrent abuse of alcohol or other central nervous system depressants. Therefore, there is a public health benefit for an abuse-deterrent formulation to be introduced into the market that cannot be insufflated, injected, or chewed.

List Submissions being reviewed (table):

Submitted data	Description	Submission Date
Section 3.2.P.2 Pharmaceutical Development Report	Dissolution method development part	10/21/2016 03/23/2017

Section 5.3.1.2 Study O-ARIR-003	Single-dose comparative bioavailability of Oxycodone ARIR versus ROXICODONE and food effect study using the highest strength tablet, 30 mg	10/21/2016
Section 1.11.1 Quality Information Amendment	Quality Information Amendment (SN0015, 2017March 17; SN0016, 2017Mar23) Response to Review Issues Identified - Biopharmaceutics	03/17/2017 03/23/2017
Section 3.2.P.5.1	Specifications	03/17/2017
Section 3.2.P.5.4	Batch analysis	10/21/2016

Review Summary: ADEQUATE

Dissolution Method and Acceptance Criterion

The proposed dissolution method listed in the following table is ADEQUATE. The Applicant accepted FDA recommended acceptance criterion listed in the table below. The Applicant accepted the recommended dissolution acceptance criterion on a submission dated March 27, 2017.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	50 rpm	500 mL	37°C ± 0.5°C	0.1 N hydrochloric acid	Amount of Oxycodone Hydrochloride Dissolved: NLT (b) (4)% at 30 minutes for 30mg, 15 mg and 5 mg of Oxycodone ARIR tablets

The selection of the medium (0.1N hydrochloric acid) was based on the aim of developing a discriminating dissolution method to be predictive of *in vivo* performance. A pilot comparative bioavailability study was conducted to assess and confirm the discriminating capability of the dissolution method. The discriminating capability of the dissolution method is also supported by data showing different release rates due to the variations in drug product formulation (e.g., (b) (4) (b) (4)).

It was observed that the release rate for all three registration batches for oxycodone ARIR (15 mg) is slower compared with 5 mg and 30 mg strengths. (b) (4)

(b) (4)

As suggested by the Agency, the Applicant used PBPK modeling and simulation to support (b) (4) acceptance criterion for 15 mg. However, due to the complexity of the population (e.g., normally distributed gastric transit time population versus non-normally distributed), an in vitro/in vivo relationship (IVIVR) model has not been established. As such, PK parameters have not been predicted for a RoxyBond product that has an in vitro dissolution profile that matches the dissolution spec of (b) (4)% (Q) at (b) (4) minutes.

Application of dissolution in QbD

The design space of (b) (4) should be set within ± (b) (4)% of target ratio (b) (4) to retain similar dissolution profiles.

Data Supporting the Approval of the Strengths not Tested In Vivo

The application does not include a biowaiver request. The approval of the lower strengths is based on the review of the in vivo bridging studies, Study O-ARIR-003 and Study O-ARIR-006. Study O-ARIR-003 is a comparative BA study for the highest strength (30 mg) to bridge to prior findings of safety and efficacy of the reference drug product (Roxicodone). Study O-ARIR-006 is a single dose proportionality study under fasted condition for all the strengths (Oxycodone ARIR 5-, 15-, and 30-mg tablets). These in vivo studies are reviewed by Office of Clinical Pharmacology.

NDA 209777 is recommended for APPROVAL from biopharmaceutics perspective.

Highlight Key Outstanding Issues from previous IR:

1. PBPK modeling and simulation results was recommended to be submitted in future NDA submissions (e.g. post approval supplements) in support of (b) (4) acceptance criterion for the proposed drug product.

Concise Description Outstanding Issues Remaining:

None.

BCS Designation

Reviewer's Assessment:

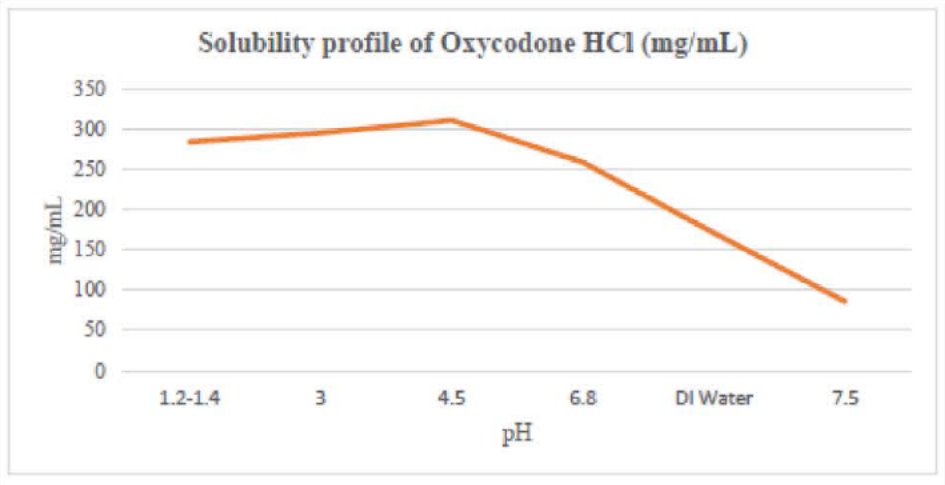
According to the Applicant, oxycodone hydrochloride is reported to be Biopharmaceutics Classification System (BCS) Class I, with high permeability and high solubility (Refer to 3.1.4 Biopharmaceutics classification in Module 3.2.P.2 Pharmaceutical Development Report).

Solubility: The aqueous solubility of oxycodone hydrochloride is high as shown in **Table 1** and **Figure 1** (refer to Table 13 in Module 3.2.P.2 Pharmaceutical Development Report).

Table 1 Solubility profile of Oxycodone HCL

pH	Solubility of Oxycodone Hydrochloride(mg/mL)	Medium
1.2-1.4	283.8	0.1 N HCl
3.0	294.9	Phosphate Buffer
4.5	310.7	Acetate Buffer
6.8	258.9	Phosphate Buffer
DI Water	170.7	DI Water
7.5	85.8	Phosphate Buffer

Figure 1. Aqueous solubility of Oxycodone Hydrochloride



Permeability:

According to the Applicant, oxycodone hydrochloride is reported to be Biopharmaceutics Classification System (BCS) Class I drug with high permeability.

There is a BCS I classification claim for oxycodone HCl (Refer to 3.1.4 Biopharmaceutics classification in Module 3.2.P.2 Pharmaceutical Development Report). There is sufficient solubility but no experimental permeability data provided to support this claim.

Information Request:

The following information request was conveyed to the Applicant in the 74 day letter.

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

Summary of the Applicant's responses dated 03/23/2017 (Module 1.11.1 Quality Information Amendment):

There is no regulatory purpose for the claim of Biopharmaceutics Classification System (BCS) class 1 for oxycodone HCl. As stated in Patent WO 2009104838 (https://www.google.com/patents/WO2009104838A1?cl=en), Oxycodone hydrochloride has a high solubility and is rapidly absorbed to the body when administered orally. Its bioavailability is 60%-87% as compared to that of direct administration into bloodstream. Although oxycodone hydrochloride is not explicitly listed in the BCS class 1, the drug exhibits a linear in vivo behavior, showing the rapid absorbance at a constant rate upon dissolution, and so, is considered the closest to BCS class 1.

Reviewer's note: The Applicant's response is acceptable.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

1. Drug Product Composition Information

Oxycodone ARIR tablets include a (b) (4) containing (b) (4), on Oxycodone ARIR (b) (4). The physical characteristics of the Oxycodone ARIR tablets are intended to provide barriers to important routes of administration common to abuse. The tablets are difficult to manipulate and resist extraction in widely used solvents. Even when manipulated with a coffee grinder, the resulting particles form a coarse powder that alters the intended release profile and rapidly forms a material that resists passage through a needle when subjected to a liquid environment. These unique properties create significant hurdles to commonly used methods of manipulation and

routes of administration for abuse. The composition of Oxycodone ARIR Tablets is shown in Table 2.

Table 2 Composition of Oxycodone ARIR Tablets

(b) (4)

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(b) (4)

2. Information about RLD

The RLD, Roxicodone (oxycodone HCl Immediate-Release tablets) was approved in August 31, 2000 (NDA021011) indicated for the management of moderate to severe pain where the use of an opioid is appropriate. The dissolution method and acceptance criteria for the RLD is shown in the following table (b) (4)

(b) (4)

3. Dissolution Method

The proposed dissolution method (refer to Table 82 in Module 3.2.P.2 Pharmaceutical Development) was shown below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Proposed Acceptance Criterion
II (paddle)	50 rpm	500 mL	37°C ± 0.5°C	0.1 N hydrochloric acid	Amount of Oxycodone Hydrochloride Dissolved: NLT (b) (4) % at (b) (4) minutes for all strengths

Except the dissolution medium, the above proposed dissolution method is similar to the USP method for Oxycodone Hydrochloride Tablets.

The Applicant submitted the following data to support the adequacy of the proposed dissolution method.

3. 1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The dissolution method development was provided in pharmaceutical development under **\\cdsesub1\evsprod\nda209777\0001\m3\32-body-data\32p-drug-prod\oxycodone-arir-tablets\32p2-pharm-dev\pharmaceutical-development-report.pdf** and dissolution method development report submitted on 03/23/2017 under **\\cdsesub1\evsprod\nda209777\0016\m3\32-body-data\32p-drug-prod\oxycodone-arir-tablets\32p2-pharm-dev\dis-method-develop-rpt.pdf)**

Selection of Medium

(b) (4)

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(b) (4)

[redacted]

Reviewer's Note: The selection of 50 rpm as rotation speed is acceptable.

3.2 What data are available to support the discriminating power of the method?

A pilot comparative bioavailability study to assess and confirm the discriminating dissolution method was conducted (Refer to part 4.6.8 development of a dissolution method based on pilot comparative bioavailability studies on page 163 in Module 3.2.P.2 Pharmaceutical Development). Refer the data analysis to section 3.1.

The additional evidence for showing the discriminating power of the dissolution method is summarized in Section "Application of dissolution/IVIVC in QBD" in this review.

3.3 Is the proposed dissolution/release method biorelevant? What data including but not limited to IVIVC are available to support this claim?

Yes, the proposed dissolution method using 0.1N HCl as release medium is biorelevant. The supporting data is included in Module 3.2.P.2 Pharmaceutical Development. For the data analysis and reviewer's assessment, refer to section 3.1.

4. Dissolution Acceptance Criterion

The mean dissolution data (N=12 units/batch) of Oxycodone ARIR (30 mg) bio-batch (C00512) used in the pivotal clinical Study O-ARIR-003, which was conducted to demonstrate the BE of

the highest strength tablet of Oxycodone ARIR (Oxycodone ARIR 30 mg) with the RLD (ROXICODONE 30 mg) is provided in **Table 5** (refer to Module 3.2.P.5.4 batch analysis).

Table 5. Biobatch (C00512) Release Results for Oxycodone ARIR 30-mg Tablets

Table 5 Batch Release Results for Oxycodone ARIR 30-mg Tablets				
Batch Number		**C005012**	**C006513**	**C007213**
Date of Manufacture		**Nov 09, 2012**	**Oct 26, 2012**	**Jan 04, 2013**
Batch Size (Tablets)		(b) (4)		
Drug substance Batch Number		**1036X008**	**1036X008**	**1219X022**
Use		**Primary Stability, Clinical Study**	**Primary Stability**	**Primary Stability**
Test	**Acceptance Criteria**	**Results**		
Dissolution[a] (average % amount dissolved, n = 12) 5 minutes	(b) (4)			
10 minutes				
15 minutes				
30 minutes				
45 minutes				
60 minutes				

The mean dissolution data (N=12 units/batch) of Oxycodone ARIR (15 mg) registration batches was shown in **Table 6** (refer to Module 3.2.P.5.4 batch analysis).

Table 6. Batch Release Results for Oxycodone ARIR 15-mg Tablets				
Batch Number		**C006913**	**C007013**	**C007113**
Date of Manufacture		**Nov 26, 2012**	**Nov 29, 2012**	**Dec 03, 2012**
Batch Size (Tablets)		(b) (4)		
Drug substance Batch Number		**1103X003**	**1103X003**	**1103X003**
Use		**Primary Stability, Clinical Study**	**Primary Stability**	**Primary Stability**
Test	**Acceptance Criteria**	**Results**		

Dissolution[a] (average % amount dissolved, n = 12)	(b) (4)
5 minutes	
10 minutes	
15 minutes	
30 minutes	
45 minutes	
60 minutes	

The mean dissolution data (N=12 units/batch) of Oxycodone ARIR (5 mg) registration batches was shown in **Table 7** (refer to Module 3.2.P.5.4 batch analysis).

Table 7. Batch Release Results for Oxycodone ARIR 5-mg Tablets

Batch Number		**C006613**	**C006713**	**C006813**
Date of Manufacture		**Nov 15, 2012**	**Nov 17, 2012**	**Nov 21, 2012**
Batch Size (Tablets)		(b) (4)		
Drug substance Batch Number		**1036X008**	**1036X008**	**1036X008**
Use		**Primary Stability, Clinical Study**	**Primary Stability**	**Primary Stability**
Test	**Acceptance Criteria**	**Results**		
Dissolution[a] (average % amount dissolved, n = 12)	(b) (4)			
5 minutes				
10 minutes				
15 minutes				
30 minutes				
45 minutes				
60 minutes				

Based on the dissolution data shown in (b) (4) the proposed dissolution specification of NLT (b) (4)% (Q) of the labeled amount of oxycodone hydrochloride dissolved in (b) (4) minutes is too permissive for the proposed drug product, Oxycodone ARIR 30 mg. Therefore, the following

data-driven dissolution acceptance criterion is recommended: *"NLT(b) (4)% (Q) of the labeled amount of oxycodone hydrochloride dissolved in 30 minutes"*. Although the dissolution data obtained from all the three registration batches for oxycodone ARIR (5 mg) meet the recommended criterion, there is one registration batch of oxycodone ARIR (15 mg) (batch No C007113) does not meet the recommended criterion (Refer to **Table 6**). Also, the release rate for all three registration batches for oxycodone ARIR (15 mg) is slower compared with 5 mg and 30 mg strengths, which needs providing the root cause.

The individual dissolution profiles for bio-batches for Oxycodone ARIR 30 mg, 15 mg and 5 mg confirmed the recommended acceptance criterion (Table 8-10) (Refer to Module 3.2.P.2 Pharmaceutical Development, Drug Product section).

Table 8. Dissolution Profile of Oxycodone ARIR Tablets, 30 mg, Batch C005012

Table 3.2.P.2.2-8. Dissolution Profile, Oxycodone ARIR Tablets, 30 mg, Batch C005012						
Tablet No.	Results (Individual Tablet % Amount Dissolved)					
	5 min	10 min	15 min	30 min	45 min	60 min
1	19.1	45.5	65.9	92.6	94.8	95.4
2	18.8	44.8	64.3	96.5	100.3	101.1
3	18.0	44.0	64.6	94.9	98.7	99.5
4	16.8	42.1	62.6	96.2	101.0	101.1
5	15.9	43.0	64.2	97.0	101.0	101.5
6	15.6	41.7	63.3	94.4	97.7	98.1
7	16.8	41.9	62.5	101.7	109.0	109.9
8	21.0	45.8	67.5	103.3	108.6	109.6
9	20.1	44.0	65.5	104.7	112.7	113.5
10	21.1	44.5	63.0	100.0	105.7	106.3
11	21.1	46.6	67.7	96.8	99.1	99.3
12	21.8	46.8	69.0	103.5	107.9	108.4
Average	18.8	44.2	65.0	98.5	103.0	103.6
RSD	11.7	4.0	3.3	4.1	5.4	5.5
Maximum	21.8	46.8	69.0	104.7	112.7	113.5
Minimum	15.6	41.7	62.5	92.6	94.8	95.4
RSD = relative standard deviation.						

Table 9. Dissolution Profile of Oxycodone ARIR Tablets, 15 mg, Batch C006913

Table 3.2.P.2.2-11. Dissolution Profile, Oxycodone ARIR Tablets, 15 mg, Batch C006913						
Tablet No.	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
1	24.7	46.1	60.3	87.2	101.1	106.6
2	21.2	44.0	58.0	84.7	94.9	97.8
3	21.5	43.6	57.2	82.5	93.1	96.5
4	24.3	46.2	60.1	85.9	96.6	99.6
5	20.2	44.2	58.9	85.6	97.3	101.6
6	22.9	44.7	58.5	84.1	93.8	96.9
7	25.7	46.5	59.9	84.9	96.6	99.7
8	23.0	45.7	59.7	83.6	93.7	96.9
9	26.7	47.3	61.5	86.5	96.8	100.2
10	23.7	43.6	57.3	79.8	86.3	87.8
11	25.0	46.3	60.4	86.1	97.3	101.0
12	26.7	47.3	60.5	85.4	96.0	99.7
Average	23.8	45.5	59.4	84.7	95.3	98.7
RSD	8.9	3.0	2.3	2.4	3.7	4.4
Maximum	26.7	47.3	61.5	87.2	101.1	106.6
Minimum	20.2	43.6	57.2	79.8	86.3	87.8
RSD = relative standard deviation.						

Table 10. Dissolution Profile of Oxycodone ARIR Tablets, 5 mg, Batch C006613

Table 3.2.P.2.2-14. Dissolution Profile, Oxycodone ARIR Tablets, 5 mg, Batch C006613						
Tablet No.	**5 min**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
1	30.3	61.1	79.9	89.6	91.3	91.7
2	34.3	63.4	84.9	97.9	99.6	99.8
3	30.0	61.3	84.9	101.7	103.9	104.8
4	24.2	57.6	79.1	105.5	109.1	110.7
5	27.6	59.3	81.8	98.9	101.5	101.9
6	26.6	59.1	79.2	89.2	90.2	90.8
7	26.4	58.2	80.2	95.1	96.8	98.3
8	27.8	60.5	84.4	102.4	104.7	105.8
9	24.3	58.0	80.6	97.0	98.6	98.9
10	25.7	57.1	79.9	101.3	103.8	104.5
11	24.4	56.5	78.6	93.1	94.9	95.9
12	22.8	55.3	77.5	94.1	96.3	97.4
Average	27.0	59.0	80.9	97.2	99.2	100.0
RSD	12.0	3.9	3.1	5.3	5.7	5.8
Maximum	34.3	63.4	84.9	105.5	109.1	110.7
Minimum	22.8	55.3	77.5	89.2	90.2	90.8
RSD = relative standard deviation.						

The sponsor also provided a summary of the release and stability profile results for each strength, which is shown in **Table 11**.

Table 11: Summary of Release and Stability Dissolution Profile of Oxycodone ARIR Tablets, 5 mg

Table 3.2.P.5.6-1. Summary of Release And Primary Stability Dissolution Profiles													
		Results (Individual Tablet % Amount Dissolved)[a]											
		5 minutes		10 minutes		15 minutes		30 minutes		45 minutes		60 minutes	
Batch	Study	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
30 mg													
C005012[b]	Release	15.6	21.8	41.7	46.8	62.5	69.0	92.6	104.7	94.8	112.7	95.4	113.5
	Stability	15.6	24.3	37.0	48.2	53.8	69.0	83.0	104.7	89.4	112.7	90.2	113.5
C006513	Release	21.2	30.1	48.2	54.5	67.4	75.3	92.1	101.7	95.0	105.5	95.6	106.4
	Stability	22.2	31.2	50.4	62.1	70.7	83.2	93.2	100.9	93.4	104.4	94.2	103.9
C007213	Release	27.8	32.8	50.6	55.3	66.0	71.2	86.4	99.2	88.2	103.3	88.8	103.9
	Stability	20.7	34.2	46.0	61.4	64.8	80.3	87.3	99.0	88.2	102.5	89.5	100.9
15 mg													
C006913[b]	Release	20.2	26.7	43.6	47.3	57.2	61.5	79.8	87.2	86.3	101.1	87.8	106.6
	Stability	15.7	27.3	36.4	48.0	49.2	61.3	74.5	86.3	82.3	101.4	88.4	102.9
C007013	Release	21.3	28.3	41.9	46.6	54.8	59.5	75.8	83.0	82.1	95.6	84.1	99.3
	Stability	16.5	27.9	35.8	45.5	47.2	59.3	68.9	82.6	79.0	96.5	83.4	100.2
C007113	Release	21.1	27.3	41.1	47.1	53.3	59.1	75.4	83.4	84.5	95.4	87.7	99.9
	Stability	16.9	26.6	34.1	46.4	46.6	59.8	68.2	83.6	80.2	100.6	83.4	103.0
5 mg													
C006613[b]	Release	22.8	34.3	55.3	63.4	77.5	84.9	89.2	105.5	90.2	109.1	90.8	110.7
	Stability	23.7	37.3	51.9	64.0	69.7	86.3	80.4	112.5	82.7	116.0	83.3	117.4
C006713	Release	26.6	37.2	50.2	72.8	67.9	86.1	88.3	99.9	89.3	102.2	90.3	103.5
	Stability	28.9	56.0	53.6	87.5	73.6	100.1	86.8	105.3	85.4	110.6	89.0	112.4
C006813	Release	24.1	32.4	57.9	64.2	80.4	87.6	90.4	101.4	91.7	102.9	92.6	103.8
	Stability	21.7	45.7	54.5	78.6	74.2	93.8	78.5	110.8	79.0	114.0	80.1	115.0

Max = maximum individual tablet % amount dissolved; Min = minimum individual tablet % amount dissolved.
[a] = Minimum and maximum individual tablet % dissolved for release and over all stability time points for either through 6 months at 40°C/75% RH or through 18 to 24 months at 25°C/60% RH.
[b] = Batch used in clinical study.

Based on the submitted bio-batch data for all the three strengths, the Applicant was asked to provide the root cause of the above observations and alternatively to use PBPK modeling and simulation to support a (b) (4) specification for 15 mg strength. Thus, IR #1 was conveyed to the Applicant on 12/23/2017, which is listed at the end of this review.

Responses:

Responses were received on 03/17/2017 (Module 1.11.1 Quality Information Amendment \\cdsesub1\evsprod\nda209777\0015\m1\us\quality.pdf), which is summarized as below:

- GastroPlus version 9.0 was used to develop a PBPK model that closely simulated the observed geometric mean maximum drug concentration (Cmax) and area under the curve (AUC) for 30-mg Roxicodone (effectively immediate-release RoxyBond) using data from Study O-ARIR-003.
- It was observed that the gastric transit time as assessed by the value for time to maximum drug concentration (Tmax) in the study population was not normally distributed for either Roxicodone or RoxyBond O-ARIR-003.
- For the remaining population that show "normal" gastric emptying times, it was shown that dissolution rate had less of an impact on Cmax and AUC.
- A virtual BE trial was performed where 30-mg Roxicodone was compared to 30-mg RoxyBond, and the results closely matched the observed results from the actual BE trial

(Study O-ARIR-003) for the 'normal' population. Using the same virtual population, a second virtual BE trial was carried out using the 15-mg RoxyBond product (which releases slower in vitro than the 30-mg product), and in this trial, AUC passed the BE criteria.

- Due to the complexity of the population (e.g., normally distributed gastric transit time population versus non-normally distributed), an in vitro/in vivo relationship (IVIVR) model has not been established.
- As such, PK parameters have not been predicted for a RoxyBond product that has an in vitro dissolution profile that matches the dissolution spec of (b)(4)% Q at (b)(4) minutes.
- The root cause of the slower release of the 15-mg RoxyBond tablet is (b)(4) that contributes to the slower release rate.
- IDS proposes to revise the acceptance criterion for dissolution as follows:

30 mg: NLT(b)(4)% (Q) of oxycodone hydrochloride in 30 minutes
15 mg: NLT (b)(4)% (Q) of oxycodone hydrochloride in (b)(4) minutes
5 mg: NLT(b)(4)% (Q) of oxycodone hydrochloride in 30 minutes

Reviewer's note:

Based on the dissolution data for bio-batches for three strengths (30 mg, 15 mg and 5 mg) shown in Table 8 to 10, all the bio-batches pass "*NLT (b)(4)% (Q) of the labeled amount of oxycodone hydrochloride dissolved in 30 minutes*" criterion at stage 2. Therefore, the following data-driven dissolution acceptance criterion is still recommended: "*NLT (b)(4)% (Q) of the labeled amount of oxycodone hydrochloride dissolved in 30 minutes*".

The slower release of the registration batch 007113 may be due to the inappropriate quality control of this batch.

IR #2 was conveyed to the Applicant on 03/16/2017, which is listed at the end of this review.

Summary of Applicant's responses to IR#2:

In response to the NDA 209777 CMC Information Request 03/16/2017, IDS accepts FDA's proposed dissolution acceptance criterion of "NLT (b)(4)% of labeled amount of oxycodone hydrochloride dissolved in 30 minutes" for all three proposed strengths: 30mg, 15 mg and 5 mg of Oxycodone ARIR tablets.

Reviewer's note:

The Applicant's response to IR#2 is ACCEPTABLE. PBPK modeling and simulation is recommended to be submitted in the future for supporting a possible (b)(4) acceptance criterion. The dissolution method and acceptance criterion listed in the following table is acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion

II (paddle)	50 rpm	500 mL	37°C ± 0.5°C	0.1 N hydrochloric acid	Amount of Oxycodone Hydrochloride Dissolved: NLT (b)(4)% at 30 minutes for 30mg, 15 mg and 5 mg of Oxycodone ARIR tablets

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment:

- According to Applicant's responses to IR#1 received on 03/17/2017 in Module 1.11.1 Quality Information Amendment (\\cdsesub1\evsprod\nda209777\0015\m1\us\quality.pdf), the Applicant tried to establish a in silico PBPK modeling and simulation for supporting a (b)(4) specification for Oxycodone ARIR tablets (15 mg strength). However, due to the complexity of the population (e.g., normally distributed gastric transit time population versus non-normally distributed), an in vitro/in vivo relationship (IVIVR) model has not been established.
- As such, PK parameters have not been predicted for a RoxyBond product that has an in vitro dissolution profile that matches the dissolution spec of (b)(4)% Q at (b)(4) minutes.
- GastroPlus model file is recommended to be submitted for future NDA submission (e.g. NDA supplement) for supporting possible (b)(4) specification, if needed.

Refer to **Section 4. Dissolution Acceptance Criterion** for more details.

Application of dissolution/IVIVC in QbD

Reviewer's Assessment:

To justify how specific ranges of the identified CMA and CPPs were defined, the following comments were communicated in the 74 day letter:

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

Summary of the Applicant's responses dated 03/23/2017

(b)(4)

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(b) (4)

[redacted]

Reviewer's note:

- These data support that the dissolution method is discriminating. (b) (4) [redacted].

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment:

N/A. This is an immediate release dosage form, not an extended release dosage form; no in-vitro alcohol dose-dumping study is required.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment:

n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment:

n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment:

n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment:

N/A. This is an immediate release abuse-deterrent dosage form, not an extended release dosage form; no in-vitro dissolution testing for showing abuse-deterrent properties is required. Although extraction study is provided in the submission (refer to 2.3.P.2.2.3.4. Category 1 Laboratory Manipulation and Extraction Studies in module 2.3.P.2 Pharmaceutical Development), which will be reviewed by Drug Product Reviewer, Dr. Xiaobin Shen.

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment:

n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment:

n/a

Bridging of Formulations

Reviewer's Assessment:

The to-be-marketed Oxycodone ARIR formulation was the same as that used in the following two pivotal clinical studies (Study O-ARIR-003 and Study O-ARIR-006) and the pilot clinical study O-ARIR-004 (Refer to page 9 in 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods). The descriptions of these three clinical studies are shown below:

- Comparative BA study, Study O-ARIR-003, was conducted to demonstrate the BE of the highest strength tablet of Oxycodone ARIR (Oxycodone ARIR 30 mg) with the RLD (ROXICODONE 30 mg) to bridge to prior findings of safety and efficacy of the RLD.
- A single dose proportionality study under fasted condition (Study O-ARIR-006) was conducted to demonstrate that Oxycodone ARIR 5-, 15-, and 30-mg tablets were dose proportional.
- In addition, relative BA of six 5-mg (30-mg dose) of O-ARIR tablets compared to a single 30-mg tablet of O-ARIR was conducted under fasted conditions (Study O-ARIR-004).

The registration batches used in the above clinical studies are listed in the following table.

Table 2.3.P.2-1. Clinical Batch Summary		
Batch	Strength	Clinical Studies
C005012	30 mg	O-ARIR-002, O-ARIR-003, O-ARIR-004, O-ARIR-006
C006913	15 mg	O-ARIR-004, O-ARIR-006
C006613	5 mg	O-ARIR-004, O-ARIR-006

As the formulation of the bio-batches C005012, C006913 and C00613 are the same as the to-be-marketed formulation, therefore, no bridging data is needed.

Biowaiver Request

Reviewer's Assessment:

No biowaiver request is submitted.

The approval of the lower strengths is based on the review of the in vivo bridging studies, Study O-ARIR-003 and Study O-ARIR-006. Study O-ARIR-003 is a comparative BA study for the highest strength (30 mg) to bridge to prior findings of safety and efficacy of the reference drug product (Roxicodone). Study O-ARIR-006 is a single dose proportionality study under fasted condition for all the strengths (Oxycodone ARIR 5-, 15-, and 30-mg tablets). These in vivo studies are reviewed by Office of Clinical Pharmacology.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

n/a

Post-Approval Commitments

Reviewer's Assessment:

n/a

Lifecycle Management Considerations

n/a

List of Deficiencies:

Biopharmaceutics Comments sent as part of the 74-Day Letter

Comments:

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

2. Submit the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include (but not limited to) the following information:
   a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product.
   b. The dissolution data (individual, mean, SD, profiles) should be reported. The testing conditions used for each test should be clearly specified.

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

Responses: The Applicant provided responses dated 03/23/2017 to above IR in Module 1.11.1 Quality Information Amendment and Module 3.2.P.2 Pharmaceutical Development.

Reviewer's assessment: The responses are found ACCEPTABLE.

Biopharmaceutics Comments for IR #1 conveyed on 12/23/2016.

Comments:

1. The release rate for all three registration batches for oxycodone ARIR (15 mg) is slower when compared to the registration batches for the 5 mg and 30 mg strengths.. Provide root cause for the observed slower release of the 15 mg strength. . Additionally, describe the control strategies in place to ensure the observed difference in drug release rate does

not impact in vivo performance. Alternatively, provide supportive data by using verified PBPK (physiologically-based pharmacokinetics) modeling and simulation(e.g. virtual BE (bioequivalence) study) to show that the slower release rate of a dissolution profile *will* not affect the bioequivalence to the RLD (ROXICODONE). For the above purpose, we recommend the following information be submitted:

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

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

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

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

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

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

Responses: Tel-conference was held with Inspirion on January 12, 2017, discussing on the above IR#1 (refer to FDA Telephone Contact Report \\cdsesub1\evsprod\nda209777\0015\m1\us\telephone-cont-rpt-2017jan12.pdf . TCON summary was provided in the APPENDIX). However, No full responses were received by the end of

February. The Applicant's Responses were received on 03/17/2017 (refer to 1.11 Information Amendment \\cdsesub1\evsprod\nda209777\0015\m1\us\quality.pdf), partially answered the information request #1. Then IR#2 was conveyed to the Applicant dated 03/16/2017.

Biopharmaceutics Comments for IR #2 conveyed on 3/16/2017:

Comment (3/16/2017)

1. We make reference to the information request letter dated December 23, 2016 and the responses received on March 15/17, 2107 on the following:

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

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

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

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

iv. The methodological approach to model verification, model verification results, and sensitivity analyses to evaluate the robustness of the model should

be clearly presented. Note that it is generally expected that the clinical data will contribute to establish confidence in the appropriateness of the model in addressing the study question(s).

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

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

In order to continue the review of your submission, we request that you submit a full report and the project file which includes all input and outputs generated during model development, validation and application responses by Monday March 20, 2017. In addition Note that if details (full report and individual data) on the PBPK modeling and simulations results are not available, we recommend that you accept the dissolution acceptance criterion of "NLT (b)(4)% of labeled amount of oxycodone hydrochloride dissolved in 30 minutes" for all three proposed strengths: 30mg, 15 mg and 5 mg of Oxycodone ARIR tablets. Note that if applicable, you still have the possibility to submit the PBPK modeling and simulation results in future submission to the NDA (e.g. post approval supplements) in support of (b)(4) acceptance criterion for your proposed drug product.

2. Provide the root cause for the differences observed in the dissolution data between bio-batch for 15 mg Oxycodone ARIR tablets (Batch No. C006913) and other two exhibition batches (Batch no. C007013 and C007113), especially batch C007113. For example, for batch C006913, the average dissolved amount of oxycodone at 30 minutes is (b)(4)% (> (b)(4)%), while for batch C007113, the average dissolved amount of oxycodone is (b)(4)% (less than (b)(4)%) at 30 minutes. Based on the root cause analysis, tighter in process controls may be needed to avoid the variability observed in the dissolution profiles.

In response to the IR#2, the Applicant provided an email response dated 03/21/2017, partially cited as below:

"In response to the NDA 209777 CMC Information Request 3-16-17 IDS accepts FDA's proposed dissolution acceptance criterion of "NLT(b)(4)% of labeled amount of oxycodone hydrochloride dissolved in 30 minutes" for all three proposed strengths: 30mg, 15 mg and 5 mg of Oxycodone ARIR tablets. We are supplying this short response by e-mail in order to meet the request to respond by COB Monday, March 20, 2017.

We will provide the full response to both e-mail information requests via an official submission to the NDA by March 29, 2017."

Reviewer's assessment: The responses are found ACCEPTABLE. The Applicant accepted the recommended dissolution acceptance criterion on a submission dated March 27, 2017. .

Primary Biopharmaceutics Reviewer Name and Date:

Fang Wu, Ph. D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drugs Products

Date:
3/25/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Sandra Suarez, Ph. D.
Secondary Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drugs Products
Date: 03/27/2017

APPENDIX

NDA 209777 Teleconference Summary

Date: January 12, 2017

Sponsor: Inspirion Delivery Services

PM: Taiye Ayoola

FDA Attendees:

Fang Wu, Biopharmaceutics Reviewer, PhD, Division of Biopharmaceutics/ONDP/OPQ/CDER

Kimberly Raines, Branch Chief (Acting), PhD, Division of Biopharmaceutics/ONDP/OPQ/CDER

Ciby Abraham, PhD, Acting Team Leader, ONDP/OPQ/CDER

Anjelina Pokrovnichka, Medical Officer, DAAAP

Taiye Ayoola, PharmD, Regulatory Project Manager, DAAAP

Mavis Darkwah, PharmD, Regulatory Project Manager, DAAAP

Inspirion Attendees:

(b) (4), Regulatory/Nonclinical Consultant, (b) (4)

(b) (4) CMC Consultant, (b) (4)

(b) (4), Clinical Consultant, (b) (4)

Matthew Iverson, Vice President, Clinical Development, IDS

Carmela Pantaleon, Director, Clinical Development, IDS

Ray DiFalco, President, IDS

Major meeting content:

1. The Applicant asked about why the proposed dissolution specification (b) (4)% at (b) (4) minutes) is not acceptable.
   Answer: Because we would like to see the complete release of the drug from the formulation (release over (b) (4)%) and we set specification based on the dissolution data of bio-batches for 30mg, 15 mg and 5 mg strengths. Based on the dissolution data for the

bio-batches, they all meet "NLT (b)(4)% at 30 minutes" acceptance criterion. For the 15 mg strength, bio-batch meet "NLT (b)(4)% at 30 minutes", however, there is one registration batch does not meet the above criterion. The Applicant should either accept "NLT (b)(4)% at 30 minutes" acceptance criterion or provide supportive evidence such as in silico modeling to support another proposed acceptance criterion.

2. Will the Agency accept the different acceptance criterion for different strength?
   Answer: In general, we could accept different acceptance criterion for different strength, however, that will be based on the totality of the submitted data.

3. The Applicant are developing models, will the end of February acceptable for providing the model files?
   Answer: If possible, mid of February would be a good timeline for submitting the model report and model files.

   The Applicant said that they will submit the model ASAP.

4. If the Agency has the experiences of developing the model, can the Agency share the model files or related information?
   Answer: We do not have any data to share at the moment.

Sandra Suarez

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Fang Wu

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PROCESS

Product Background:	
NDA/NDA:	**209777**
Drug Product Name / Strength:	**RoxyBond (Oxycodone ARIR) Oxycodone HCl; 5, 15, 30mg immediate release tablets**
Route of Administration:	**Oral**
Applicant Name:	**Inspirion Delivery Sciences, LLC**

Review Summary:	
List Submissions being reviewed (table):	**SN0001 dated 10/21/2016** **SN0010 dated 2/3/2017**
Highlight Key Outstanding Issues from Last Cycle:	**No outstanding issues remain**
Concise Description Outstanding Issues Remaining:	**First cycle deficiencies are resolved see at the end of review**

P.3 Manufacture

(b) (4)

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Tarun Mehta

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Ubrani Venkataram

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Comments: Thanks

DRUG PRODUCT

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Julia Pinto

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Xiaobin Shen

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Recommendation: Approval

NDA 209777
Review #1

Drug Name/Dosage Form	RoxyBond (Oxycodone ARIR)(Oxycodone hydrochloride)/Immediate-release tablets
Strength	5, 15, and 30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Inspirion Delivery Sciences, LLC
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Stevens	OPQ/ONDP/DNDPAPI/BII
Drug Product	Xiaobin Shen	OPQ/ONDP/DNDPII/BIV
Process	Tarun Mehta	OPQ/OPF/DPAII/BVI
Microbiology	Tarun Mehta	OPQ/OPF/DPAII/BVI
Facility	Daniel DiCiero	OPQ/OPF/DIA/BII
Biopharmaceutics	Fang Wu/Sandra Suarez	OPQ/ONDP/DB/BIII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Ciby Abraham	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	3/26/17	Sufficient information provided in NDA
	Type II			Adequate	3/28/17	
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type IV			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA
	Type III			Adequate	3/26/17	Sufficient information provided in NDA

(b) (4)	Type IV	(b) (4)	Adequate	3/26/17	Sufficient information provided in NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Right of Reference for PT	NDA 206544	

2. CONSULTS - None

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, biopharmaceutics, process, microbiology, facilities, and drug product, CMC recommends the approval of Roxybond 5 mg, 15 mg, and 30 mg immediate release tablets.

II. Summary of Quality Assessments

The drug substance, Oxycodone HCl is manufactured by [redacted] and is referenced in DMF# [redacted] (adequate, last reviewed 5/19/2016). Oxycodone is a white [redacted] powder. The drug substance has a [redacted] month retest period when store [redacted]

Roxybond IR tablets are round, coated tablets printed with an [redacted] ink. All strengths (5, 15, and 30 mg) of Roxybond are manufactured using the same manufacturing process. [redacted] 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 between15°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.

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 [redacted] for the [redacted] 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 [redacted] of the [redacted] 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.

A. Final Risk Assessment (see Attachment)

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials	M	-	-	(b) (4)

					(b) (4)
	• Process parameters • Scale/equipment • Site				
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	-	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

III. Administrative

A. Reviewer's Signature

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
Application Technical Lead
ONDP/DIVII/Branch IV

DRUG SUBSTANCE

(b) (4)

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Donna Christner

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Ben Stevens

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