

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209819Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 209819

Review 1

Drug Name/Dosage Form	BuprenorphineSolution for injection
Strength	100 mg and 300 mg
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Indivor, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	30-May-2017	Drug Substance, Drug Product, Process, Facilities, Biopharm, Micro
Amendment (SD #8)	13-Jul-2017	Facilities
Amendment (SD #12)	11-Aug-2017	Drug Product, Micro
Amendment (SD #13)	18-Aug-2017	Drug Product, Process, Facilities, Biopharm
Amendment (SD #14)	25-Aug-2017	Drug Product, Process, Facilities, Micro
Amendment (SD #15)	1-Sep-2017	Drug Product, Process, Facilities
Telecon (SD #16)	18-Sep-2107	Drug Product, Facilities
Amendment (SD #20)	20-Sep-2017	Drug Substance, Drug Product, Process, Facilities, Biopharm, Micro
Amendment (SD #22)	29-Sep-2017	Drug Product, Process, Biopharm
Amendment (SD #27)	17-Oct-2017	Drug Substance, Drug Product, Micro
Teleconference	25-Oct-2017	Drug Product, Biopharm
Amendment (SD #29)	30-Oct-2017	Drug Product, Biopharm
Amendment (SD #30)	1-Nov-2017	Biopharm
Amendment (SD #31)	3-Nov-2017	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Fred Burnett	Donna Christner
Drug Product	Valerie Amspacher	Julia Pinto
Process	Sri Rama Krishnaiah Yellela	Pei-I Chu
Microbiology	Jonathan Burgos	Erika Pfeiler
Facility	Frank Wackes	Christina Capacci-Daniel
Biopharmaceutics	Sandra Suarez	Haritha Mandula
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	Ciby Abraham	
Laboratory (OTR)		
ORA Lead	Caryn McNab	
Environmental		

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	3 Nov 2017	Sufficient information provided in NDA
	Type III		Adequate	3 Nov 2017	Sufficient information provided in NDA	
	Type III		Adequate	3 Nov 2017	Sufficient information provided in NDA	
	Type III		Adequate	The (b) (4) procedure reviewed by micro (M. Cruz-Fisher 18 May 2016)	Reviewed previously and no revision since last review	
	Type III		Adequate	3 Nov 2017	Sufficient information provided in NDA	
	Type III		Adequate	3 Nov 2017	Sufficient information provided in NDA	
	Type IV		Adequate	22 Aug 2017	(b) (4) Reviewed method validation	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20723	Subutex® (Buprenorphine Hydrochloride)

2. CONSULTS – N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

[IQA Review Guide Reference](#)

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, process, biopharmaceutics, microbiology, facilities, and drug product, CMC recommends the approval of Sublocade 100mg and 300 mg solution for injection.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	<p>Sublocade is indicated for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product.</p> <p>Sublocade should be used as part of a complete treatment program that includes counseling and psychosocial support.</p>
Duration of Treatment	Sublocade is administered monthly only by subcutaneous injection in the abdominal region.
Maximum Daily Dose	300 mg once monthly.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

The drug substance buprenorphine is manufactured by Indivior UK Limited.
 Buprenorphine is a white to pale cream powder (b) (4)
 The buprenorphine base drug substance (b) (4)
 is stored (b) (4)
 The retest period is (b) (4)
 months when the API is stored at (b) (4)

The drug product Sublocade is a sterile, non-aqueous solution for subcutaneous injection indicated for the treatment of opioid use disorder. It contains 100 mg or 300

mg of buprenorphine (buprenorphine base) in the ATRIGEL[®] Delivery System, which is designed to deliver buprenorphine over a minimum of 28 days after subcutaneous injection. Sublocade is composed of a biodegradable 50:50 poly(DL-lactide-co-glycolide) polymer (PLGH),^{(b) (4)} The N-methyl-2-pyrrolidone (NMP),^{(b) (4)}

is released from the depot by diffusion.

. Buprenorphine
^{(b) (4)}

During the review cycle, CMC identified a^{(b) (4)} throughout stability. The applicant initially proposed^{(b) (4)} After extensive discussions with clinical pharmacology and the medical team, we concluded that the specification of^{(b) (4)} would be adequate for release and stability of the product. The specification was justified based on human PK data from the clinical trials. The applicant placed^{(b) (4)} specification for^{(b) (4)} to ensure that the product will be within^{(b) (4)} throughout its shelf-life.

A sterile^{(b) (4)} syringe is used for the primary packaging of the 100 mg and 300 mg Sublocade product. Each assembled syringe and an oxygen absorber are placed into a labeled foil-laminate pouch and heat-sealed. Each pouched unit is placed in a labeled^{(b) (4)} carton along with a sterile safety needle and labeling. The applicant provided an adequate extractables/leachables assessment for the product.

The drug product is^{(b) (4)} based on the stability data provided, an 18-month expiry is granted when stored at 2°C to 8°C (35.6°F to 46.4°F). Once the product is removed from the refrigerator, the drug product may be stored in its original packaging at room temperature (15°C to 30°C/59°F to 86°F) for up to 7 days prior to administration.

C. Final Risk Assessment

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	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	-	N/A	-
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	-	N/A	-
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	-	N/A	-
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment 	L	-	-	-
In Vitro Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping 	L	-	-	-



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BIOPHARMACEUTICS

Product Background:

NDA: 209819 ORIG-1

Drug Product Name / Strength: Buprenorphine-Atrigel, 100 mg and 300 mg

Route of Administration: Subcutaneous injection in the abdominal region

Applicant Name: Indivior

The Applicant is seeking approval of Buprenorphine-Atrigel for the monthly treatment of moderate to severe opioid use disorder (OUD). Buprenorphine-Atrigel (also referred in here as RBP-6000) is a single entity combination product (drug/device), accessible in a prefilled syringe containing buprenorphine in the ATRIGEL drug delivery system. RBP-6000 is a subcutaneously injected, extended-release sterile product of buprenorphine base in the well-established- ATRIGEL® Delivery System. The ATRIGEL Delivery System is a non-aqueous solution consisting of a biodegradable polymer and a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The RBP-6000 formulation is a solution of buprenorphine (18% w/w) and PLGH in NMP. RBP-6000 forms a depot when injected subcutaneously and releases buprenorphine for a minimum of 28 days as the polymer biodegrades. The drug product is provided in doses of 100 mg and 300 mg strengths.

Buprenorphine has been approved for multiple indications and routes of administration (e.g., sublingual, buccal, intramuscular, intravenous, transdermal, rectal and subdermal) by various manufacturers. In the USA, Indivior markets buprenorphine HCl in combination with naloxone as SUBOXONE® SL film (for SL or buccal use) for the treatment of opioid dependence. In other countries, Indivior markets SUBUTEX® (buprenorphine only) and SUBOXONE® (buprenorphine/naloxone) SL tablets for the same indication.

This application is being filed as a 505(b)(2) as it relies on published literature to support the safety assessment of the excipients which form the ATRIGEL delivery technology. The clinical pharmacology and pharmacokinetics (PK) of RBP-6000 were evaluated in 7 clinical studies in subjects with OUD to assess single-dose and multiple-dose PK, to assess exposure-response relationships for achieving efficacy and to evaluate buprenorphine potential to prolong QT interval. The manufacturing site for the commercial formulation and the pivotal clinical trial batches is the same (b) (4). Fast Track designation was granted by the Agency on May 23, 2016.

Review Summary:

The Buprenorphine-Atrigel (RMP-6000) delivery system is a solution of buprenorphine (18% w/w) and PLGH in NMP. RBP-6000 forms a depot when injected subcutaneously and releases buprenorphine for a minimum of 28 days as the polymer biodegrades. The drug

product is provided in doses of 100 mg and 300 mg strengths. The two strengths are proportionally similar in composition and in vivo PK dose-proportionality and efficacy/safety data were included in the submission in support of their approval. The in vivo dose-proportionality data is under the purview of OCP. The Atrigel delivery system has been designed to be administered on a monthly basis and is proposed to be marketed as an extended release drug product. In vitro and in vivo PK data support the ER designation claim.

The drug product underwent some manufacturing changes through the phases of development, which are considered minor for this ER drug product. Specifically, a change in the ^{(b) (4)} process was introduced for Phase 3 batches. Since the efficacy and safety assessment is based on phase 3 trials which used the ^{(b) (4)} process, the changes implemented during phase 2 are considered not clinically relevant and are acceptable from biopharmaceutics perspective. Based on an internal discussion with the product reviewer and on the results provided by the Applicant, the reviewer agrees that the changes implemented to the pivotal clinical trial formulation (e.g. ^{(b) (4)} procedures) are considered minor with no additional data requirement.

The following in vitro release method and acceptance criteria were agreed upon (refer to submission dated Nov 1, 2017):

IVR Time Point	Acceptance Criteria*
1 hour	^{(b) (4)} %
24 hours	^{(b) (4)} %
48 hrs	NLI ^{(b) (4)} %
64 hours	NLT ^{(b) (4)} %

*All batches should conform according to USP <711> at release and during stability testing

The drug product specification set for the critical quality attributes (e.g. (b) (4)) are considered clinically relevant based on a “clinical safe space” constructed by the reviewer using a mapping approach/IVIVR. Specifically, based on the results of PK Study 0006 and risk assessment/communication with the CMC, clinical and clinical pharmacology review teams, the extremes of release rate allowed by the dissolution acceptance criteria ranges will ensure that the batches performing within this range will have similar in vitro and in vivo performance as that observed for the pivotal clinical batches.

Given the importance of (b) (4) as a critical attribute affecting the in vitro release and in vivo performance, the Applicant was requested during the review cycle to revise their proposed ranges. The following acceptance criterion for (b) (4) has been agreed upon (refer to submission dated 10/30/17): (b) (4) at release. From Biopharmaceutics perspective, the proposed control strategy (b) (4) are acceptable to assure product quality and in vivo performance; *however, given that* (b) (4) *may be affected by factors other than* (b) (4) *, it is recommended to be monitored at release and through stability (e.g.* (b) (4) *).*

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
5/30/17	001
08/18/17	012
09/20/17	019
09/29/17	021
10/30/17	028
11/01/17	029

Highlight Key Outstanding Issues from Last Cycle: NONE

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 209819 for Buprenorphine Atrigel™ Delivery System, 100 mg and 300 mg is recommended for Approval.

Drug Product

RBP-6000 drug product is a sterile, non-aqueous solution for subcutaneous injection indicated for the treatment of opioid use disorder. It contains 100 mg or 300 mg of buprenorphine (buprenorphine base) in the ATRIGEL® Delivery System, which according to the Applicant, is designed to deliver buprenorphine over a minimum of 28 days after subcutaneous injection. The ATRIGEL Delivery System is composed of a biodegradable 50:50 poly(DL-lactide-coglycolide) polymer (PLGH), (b) (4), and N-methyl-2-pyrrolidone (NMP), a biocompatible solvent, (b) (4).

(b) (4)

According to the Applicant, buprenorphine is released from the depot by diffusion.

(b) (4)

(b) (4)

Drug Substance
BCS Designation

The pH solubility profile for buprenorphine is shown in Table 1.

pH of buffer	Concentration of buprenorphine free base (mg/mL)
1.3	0.25
2.0	0.20
3.0	0.21
4.0	0.20
5.0	0.08
6.0	0.02
7.0	<0.01
8.0	<0.01
9.1	<0.01

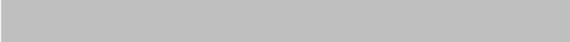
Buprenorphine is considered a low water solubility compound. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. This information is leveraged in support of biowaiver for orally administered drug products. Therefore, BCS class for this drug product is not relevant since it is to be administered via subcutaneous (SC) route.

(b) (4)



IVR Discriminating Ability

The discriminating ability of the method was evaluated against the following critical quality attributes using batches manufactured at smaller R&D scale:

1.  (b) (4)
2. 
3. 

The sensitivity of the method  (b) (4) demonstrate that the method can effectively evaluate changes in product over the course of its shelf-life (Figure 4) using the proposed regulatory method. Changes in  (b) (4)

(b) (4)% and (b) (4) composition did not have a significant impact on drug product release (data not shown in here; refer to report number FC-RPT-0039.01 for more details).

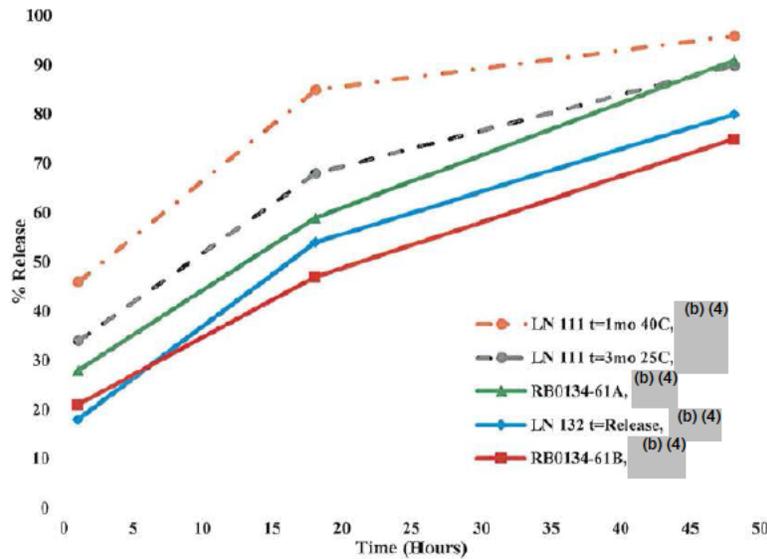


Figure 4: Effect of (b) (4) on % Release (RB0074-30, RB0102-10, RB0132-83).

Reviewer’s Comment

The proposed method is not a conventional USP method but is consistent to the methodology used for similar dosage forms. Given that the method is reproducible and found appropriate (refer to CMC review for method validation) with discriminating capability (see section below), the method is deemed acceptable.

IVR Acceptance Criteria

The following acceptance criteria were originally proposed for the drug product under review. According to the Applicant, the data supporting these criteria are shown in Figure 5.

IVR Time Point	Acceptance Criteria
(b) (4)	



Figure 5: Typical IVR profiles for clinical pivotal batches.



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Therefore, implement the following in vitro release acceptance criteria and submit an updated table of specification reflecting this change:

IVR Time Point	Acceptance Criteria*
1 hour	(b) (4) %
24 hours	(b) (4) %
48 hrs	NLT (b) (4) %
64 hours	NLT (b) (4) %

*All batches should conform according to USP <724> at release and during stability testing

The Applicant agreed with the above recommendation on a submission dated Nov 1, 2017.

Reviewer’s Assessment: ADEQUATE

The data provided demonstrated that the in vitro release method along with the recommended acceptance criteria are discriminating against critical quality attributes (b) (4)

(b) (4), and will ensure consistent in vitro and in vivo performance of the drug product throughout its life cycle.

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

Reviewer's Assessment: ADEQUATE

A (b) (4) IVIVC was attempted by the Applicant using population PK analysis following SC injection of RBP-6000. (b) (4) IVIVC could not be established, (b) (4)

However, the reviewer, constructed a "clinical safe space" using a mapping approach/IVIVR. (b) (4)

and risk communication/assessment with the clinical and clinical pharmacology review teams the extremes of release rate allowed by the dissolution acceptance criteria ranges will ensure that the batches performing within this range will have similar in vitro and in vivo performance as that observed for the pivotal clinical batches.

(b) (4)

Reviewer's Assessment: ADEQUATE

From Biopharmaceutics perspective, the proposed control strategy (including the in process controls attributes/parameters) are acceptable to assure product quality and in vivo performance; however, given that (b) (4) may be affected by factors other than (b) (4), it is recommended its monitoring at release and through stability (e.g. (b) (4)).

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping**Reviewer's Assessment: NA**

This drug product is to be administered parenterally, and therefore, in vitro alcohol dose-dumping assessment is not applicable.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

During the review cycle, the Applicant was requested to provide evidence of extended release characteristics of their proposed product based on the following:

1. A bioavailability (BA) profile established for the drug product that rules out the occurrence of any dose dumping.
2. Data supporting that the drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that was approved as an NDA.
3. Data supporting that the drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.
4. Data supporting that the drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

On a submission dated 08/18/17, the Applicant provided sufficient information (summarized) as follows to support that their proposed product has ER characteristics:

1. A bioavailability (BA) profile established for the drug product that rules out the occurrence of any dose dumping.

PK data in the Phase 3 program did not show any evidence of dose dumping. Extensive PK sampling was performed (> 13,000 PK observations) in the double-blind efficacy Phase 3 study (13-0001) and open-label long-term safety Phase 3 study (13-0003). Plasma concentrations were very consistent across time and subjects. No outlier PK profile was observed (Figure 9).

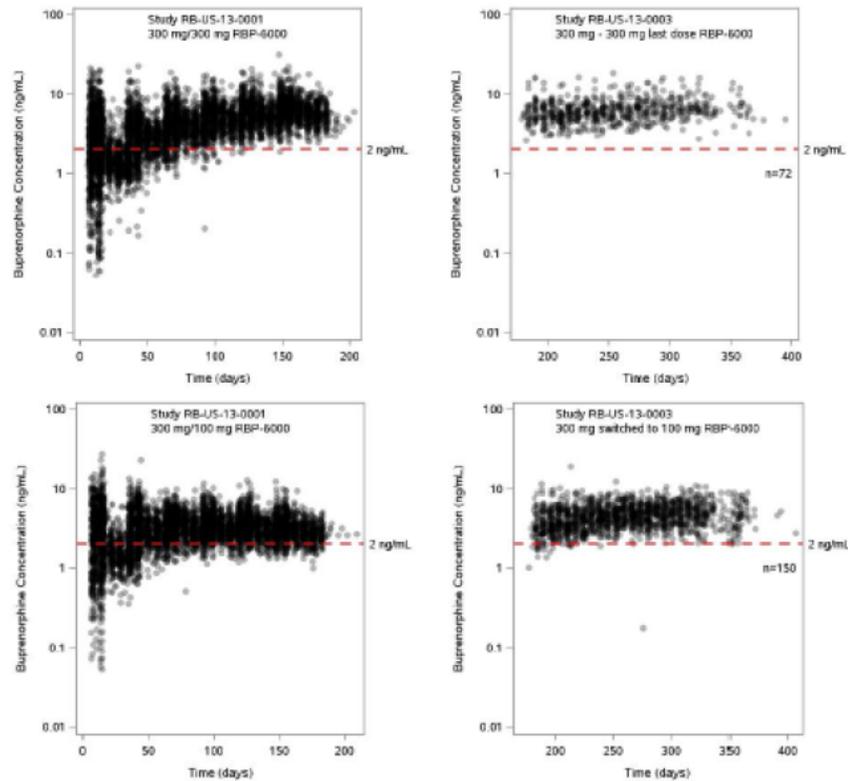


Figure 9: Buprenorphine Plasma Concentrations After Repeated SC Injections of RBP-6000 in Phase III Double-blind (13-0001) and Long-term Safety (13-0003) Studies.

- 2. Data supporting that the drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that was approved as an NDA.**

According to the Applicant, the PK parameters of buprenorphine after repeated doses were compared between RBP-6000 (100 mg and 300mg monthly dosing regimens) and currently marketed sublingual (SL) buprenorphine products (SUBUTEX; SUBOXONE Film or Tablet; daily dosing regimen). Fluctuation in plasma concentrations were much lower for RBP-6000 (43 to 116%) compared to SL buprenorphine products (223 to 305%) (Table 7).

Table 7: Comparison of Buprenorphine Mean PK Parameters between RBP-6000 (100 mg and 300 mg) and SL Buprenorphine Formulations (8–24 mg)

Formulation	Study	Dose (mg)	Cohort	N	C _{max} (ng/mL)	C _{avg} (ng/mL)	C _{min} (ng/mL)	Fluctuation (%)
SUBUTEX SL Tablet	12-0005 (MAD)	8	1	15	3.52	1.19	0.52	252
		8	4	15	3.96	1.25	0.57	271
		12	2	15	5.35	1.71	0.81	265
		14	5	15	5.26	1.95	0.92	223
	24	3	15	7.57	2.63	1.39	235	
	CR96/008 (Historical)	16	-	17	7.94	2.28	1.32	290
		24	-	15	11.88	3.38	1.90	295
32		-	10	18.09	4.90	3.16	305	
SUBOXONE SL Tablet	11-0020 (SAD)	12	4	13	4.32	1.43	0.74	250
SUBOXONE Film	13-0006 (MW)	12	all	47	6.33	1.87	0.80	296
RBP-6000	13-0001 (Phase III)	100	12 SC injections (model)	194	3.91	2.98	2.63	43
		300	12 SC injections (model)	196	10.29	7.78	6.74	46
		100	6 SC injections (model)	194	4.11	3.14	2.74	44
		300	6 SC injections (model)	196	8.68	6.32	5.11	56
	12-0005 (MAD)	100	2	12	3.07	1.89	1.26	96
		100	4	8	2.55	1.90	1.18	72
		300	6	7	9.64	4.81	4.04	116

Source: Table 16 of Module 2.7.2

MAD= multiple ascending dose; MW= molecular weight; SAD= single ascending dose

CR96/008= Historical data (C_{avg} was calculated as reported AUC_{0-24h} divided by 24)

% Fluctuation was calculated as $[(C_{max}-C_{min})/C_{avg}] \times 100$

3. Data supporting that the drug product’s formulation provides consistent pharmacokinetic performance between individual dosage units.

The Applicant claims that the PK of buprenorphine after SC injection of 300 mg or 100 mg RBP-6000 was found to be consistent across the clinical program, and the mean buprenorphine concentration-time curves obtained in the different clinical studies were almost superimposable after single and multiple injections. The conclusion reached was that these data demonstrated RBP-6000 delivered consistent PK performances across the entire clinical program (Figure 10, showing only the 300 mg strength).

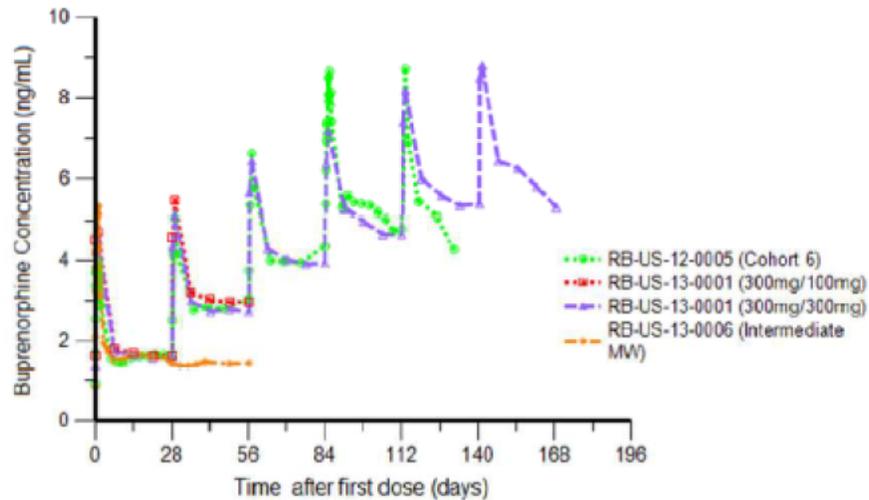


Figure 10. Mean Buprenorphine Plasma Concentration-Time Profiles for 300 mg RBP-6000 Across the Different Clinical Studies.

Reviewer’s Assessment: ADEQUATE

The data provided above including the fact that RBP-6000 has been designed to be administered on a monthly basis while current transmucosal (sublingual/buccal) immediate-release formulations of buprenorphine are administered on a daily basis, support the extended release designation claim for Buprenorphine- Atrigel.

Bridging of Formulations throughout the Phases of Drug Product Development

According to the Applicant, throughout development, the RBP-6000 manufacturing process has consisted of (b) (4)

. Over the course of development, changes were focused in optimizing the RBP-6000 manufacturing process. Essentially, 2 manufacturing processes were utilized during development. (b) (4)

The Applicant claims that any other changes from clinical to commercial drug product were minor process improvements (Table 9). In addition, results from pharmacokinetic studies in dogs showed that there are no appreciable differences in product performance (b) (4)

Table 8: Lots Manufactured by Each Manufacturing Process and Use

Drug Product Lot Number / Strength	Contract Manufacturing Organization Lot Number	Manufacturing Process	Use
Lot 111 / 200 mg	(b) (4)	1	Phase 1 Clinical Study RB-US-10-0011
Lot 132 / 200 mg	(b) (4)	1	Phase 2 Clinical Study RB-US-11-0020 Phase 2 Clinical Study RB-US-12-0020
Lot 133 / 200 mg	(b) (4)	1	Phase 2 Clinical Study RB-US-13-0002 Phase 2 Clinical Study RB-US-12-0005
Lot 161 / 300 mg	(b) (4)	2	Late Phase 1 Clinical Study RB-US-13-0006
Lot 162 / 300 mg	(b) (4)	2	Late Phase 1 Clinical Study RB-US-13-0006
Lot 158 / 100 mg	(b) (4)	2	Phase 3 Clinical Study RB-US-13-0001
Lot 160 / 300 mg	(b) (4)	2	Phase 3 Clinical Study RB-US-13-0001
Lot 184 / 300 mg	(b) (4)	2	Phase 3 Clinical Study RB-US-13-0001 Phase 3 Clinical Study RB-US-13-0003 Late Phase 1 Clinical Study RB-US-13-0006
Lot 186 / 100 mg	(b) (4)	2	Phase 3 Clinical Study RB-US-13-0001 Phase 3 Clinical Study RB-US-13-0003
Lot 192 / 100 mg	(b) (4)	2	Primary Stability
Lot 193 / 100 mg	(b) (4)	2	Primary Stability
Lot 194 / 100 mg	(b) (4)	2	Primary Stability
Lot 195 / 300 mg	(b) (4)	2	Primary Stability
Lot 196 / 300 mg	(b) (4)	2	Primary Stability Phase 3 Clinical Study RB-US-13-0003
Lot 197 / 300 mg	(b) (4)	2	Primary Stability Phase 3 Clinical Study RB-US-13-0003
210A / 300 mg	(b) (4)	2	Post-primary stability packaging and process improvement lots
213A / 100 mg	(b) (4)	2	Post-primary stability packaging and process improvement lots

Table 9: Schematic overview of formulation development**Reviewer's Assessment: ADEQUATE**

A change in the (b) (4) process was introduced for Phase 3 batches. According to the Applicant, this change did not affect the in vivo performance of the drug product. However, this conclusion was based on preclinical data (dog data). Nevertheless, since the efficacy and safety assessment is based on phase 3 trials which used the (b) (4) process, the changes implemented during phase 2 are considered not clinically relevant and are acceptable from biopharmaceutics perspective. Based on an internal discussion with the product reviewer and on the results provided by the Applicant, the reviewer agrees that the changes implemented to the pivotal clinical trial (e.g. (b) (4)) are consider minor with no additional data requirement. The manufacturing site for the commercial formulation and the pivotal clinical trial batches is the same (b) (4).

Data Available Supporting the Approval of Lower Strengths**Reviewer's Assessment: NA**

An in vivo study (clinical PK) was conducted to determine the dose-proportionality between the 100 mg and 300 mg strengths. These data are being reviewed by OCP team. From in vitro perspective, data was shown that the two strengths have superimposable in vitro release profiles in the proposed QC medium (Figure 3)

Biowaiver Request**Reviewer's Assessment: NA**

See section above on bridging.

R Regional Information***Comparability Protocols*****Reviewer's Assessment: NA*****Post-Approval Commitments*****Reviewer's Assessment: NA*****Lifecycle Management Considerations***

The proposed control strategy is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, during the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g., SUPAC Level 3 process change).

List of Deficiencies: NONE pending.***Primary Biopharmaceutics Reviewer Name and Date:****Sandra Suarez Sharp, Ph.D. (Branch 2DB\ONDP\OPQ), Oct 31, 2017****Secondary Reviewer Name and Date (and Secondary Summary, as needed):****Mandula Haritha, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ), 11/2/2017*

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Suarez

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MICROBIOLOGY

Product Background:

NDA/ANDA: 209819

Drug Product Name / Strength: RBP-6000 (Buprenorphine-ATRIGEL),
100 mg/Syringe and 300 mg/Syringe

Route of Administration: Subcutaneous Injection

Applicant Name: Indivior, Inc.

Manufacturing Site:



(b) (4)

Method of Sterilization:



(b) (4)

List Submissions being reviewed (table):

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
05/30/2017	05/30/2017	N/A	06/01/2017
08/11/2017	08/11/2017		08/11/2017
08/25/2017	08/25/2017		08/29/2017
9/20/2017	9/20/2017		9/21/2017
10/17/2017	10/17/2017		10/19/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents:

DMF  (b) (4) Reviewed and found adequate by M. Cruz-Fisher in  (b) (4), dated in 18 May 2016.

DMF  (b) (4) Reviewed and found adequate by J. Burgos  (b) (4) dated 10 October 2017.

P.2.5 Microbiological Attributes

N/A

Container/Closure and Package Integrity

A total of four CCIT analyses were presented, including high voltage leak detection (HVLD), vacuum decay, dye ingress, and microbial immersion. However, only data from the microbial immersion assessments, conducted with the proposed production container/closure system, will be reviewed.

Bacterial Immersion: A 10^7 CFU/mL *Brevundimonas diminuta* suspension was prepared into which 40 tryptic soy broth-pre-filled test syringes (20 from each proposed configuration) and six breached positive control syringes were immersed for 10 ± 1 minutes under vacuum conditions. The TSB syringe fill volumes were not described. Subsequently, the vacuum was released and the syringes remained submerged for an additional 5 ± 1 minutes under positive pressure. A concurrent growth promotion assessment and negative control syringes were also included in the study. Following the bacterial challenge, syringes were incubated at $30 \pm 2^\circ\text{C}$ for a minimum of 7 days. Of note, the bacterial immersion was not performed at the manufacturing facility. Syringes were originally pre-filled with TSB at the manufacturing facility, (b) (4), and then transferred to the testing facility, (b) (4). The acceptance criteria implemented during the study was: (1) The test syringes as well as negative control syringes should be devoid of bacterial growth and (2) Growth should be observed in the positive control syringes.

Date Performed	Vial Details	Total Syringes Used	Number of Sterile Syringes	Number of Non-Sterile Syringes
Not Provided	Challenged Syringes	40*	40	0
	Negative Control Syringes	6**	6	0
	Positive Control Syringes	6**	0	6
	Growth Promotion Syringes	6**	0	6

*, 40 Total Syringes Analyzed: 20 syringes from 1 mL Configuration and 20 syringes from 2.25 mL Configuration.

** , 6 Total Syringes Analyzed: 3 syringes were used in each of the syringe configuration studies.

Note to Reviewer: Additional syringes harboring differently sized capillary tubes were also included in the studies. Although the incubation conditions used to evaluate these samples were unclear, no additional information will be requested from the applicant since results from the remaining controls were adequate.

The following deficiency was issued in the 27 July 2017 filing communication:

*Comment: Regarding the bacterial immersion study performed to demonstrate container closure integrity with the 1 mL and 2.25 mL syringe configurations: Although it was indicated the test and positive control samples were challenged in a *Brevundimonas diminuta* suspension, the concentration of the bacterial suspension was not provided. Please elaborate on the bacterial concentration utilized in the container closure integrity test.*

In the 11 August 2017 response, the applicant indicated the concentration of the *Brevundimonas diminuta* used in the immersion challenge was 10^7 CFU/mL.

The information provided by the applicant was adequate.

Acceptable

Antimicrobial Effectiveness Testing

Not applicable since the drug product is provided as a single dose vial and does not contain preservatives.

P.3 Manufacture

N/A

P.3.1 Manufacturers

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)



Ciby
Abraham

Digitally signed by Ciby Abraham

Date: 11/07/2017 10:09:27AM

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