CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary NDA 210136 Assessment 5

1. Application/Product Information

NDA Number.	210136
Applicant Name	Braeburn Inc.
Drug Product Name	Buprenorphine Injection 8, 16 24, 32 mg Weekly; 64, 96, 128 mg Monthly
Dosage Form.	Injection, extended release
Proposed Strength(s)	CAM2038 q1w - 50 mg/mL buprenorphine (q1w - 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL) CAM2038 q4w - 356 mg/mL buprenorphine (q4w - 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL)
Route of Administration	Subcutaneous
Maximum Daily Dose	N/A
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of moderate to severe opioid use disorder (OUD)
Drug Product Description	50 mg/mL buprenorphine q1w subcutaneous injection depot drug product is a sterile (b) (4) yellowish to yellow clear liquid in 1 mL glass syringes with grey plungers. The q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. 356 mg/mL buprenorphine q4w subcutaneous injection depot drug product is a sterile (b) (4) yellowish to yellow clear liquid in 1 mL glass syringes with grey plungers. The q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 40/60 to final volume.
Co-packaged product information	N/A
Device information:	Pre-filled glass syringe

Storage Temperature/ Conditions	25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Valerie Amspacher	Julia Pinto
	Manufacturing	Lane Christensen	
	Biopharmaceutics	N/A	N/A
	Microbiology	Gouri Chattopadhyay	Paul Dexter
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf-life of 36 months is assigned to the drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is approval for this NDA based on reviews for drug product, process/facilities and microbiology reviews. The drug substance and biopharmaceutics reviews recommended approval in the previous review cycle and remain approval in this review cycle.

The applicant resubmitted 23 Nov 2022, this document is a review of that resubmission.
A complete response letter was issued 15 Dec 2021 due to facility issues
The applicant resubmitted 15 Jun 2021
A complete response letter was issued 1 Dec 2020 due to facility issues
The applicant resubmitted 1 Jun 2020
A tentative approval letter was issued on 21 Dec 2018
The applicant resubmitted on 26 Jun 2018
The applicant resubmitted 23 May 2018, but that submission was incomplete
A complete response letter was issued 19 Jan 2018
The NDA was originally submitted 28 July 2017

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

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FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	For the treatment of moderate to severe opioid use disorder (OUD)
NDA Number	210136
Assessment Cycle Number	03
Drug Product Name/ Strength	Brixadi/(buprenorphine) injection. 8, 16, 24, 32 mg-week; 64, 96, 128 mg-month
Route of Administration	Subcutaneous Injection
Applicant Name	Braeburn Inc.
Therapeutic Classification/ OND Division	Opioid Dependence (2030300)/ CDER/OND/ON/DAAP
Manufacturing Site	Pharmaceutics International, Inc (Pii), 10819 Gilroy Road, Hunt Valley, MD 21031 FEI # 1000513101
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Assessment Summary: The drug product is (b) (4) (b) (4) (b) (4) This application was reviewed and found microbiology adequate in August 2018. Since then, multiple resubmissions were submitted, and Microbiology review was not required. This recent submission is a Complete Response to a single deficiency related to facility and some other CMC updates.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
• NDA-210136-Resub-Amendment-143 (Seq # 0143)	• 11/23/2022
• Response to the Information Request (Seq # 0145)	• 03/03/2023

Review Cycle	List Submissions being reviewed
MR01	7/19/2017, 08/23/2017, 10/06/2017, 10/30/2017, 11/09/2017, 11/29/2017, 12/08/2017.
MR02	01/05/2018, 05/23/2018.

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The original NDA submission was reviewed in N210136MR01.docx dated 12/19/2017 (inadequate) and in N210136MR02.docx dated 8/22/2018 (adequate).

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: None

Supporting Documents:

- DMF (b) (4) reviewed in D (b) (4) M20R01.docx dated 3/19/2021 and in D (b) (4) M23R01.docx dated 01/29/2022, (b) (4) (b) (4)
- DMF (b) (4), reviewed and found adequate in D (b) (4) M07R01.docx dated 6/7/2021 and D (b) (4) M09R01.docx dated 6/27/2022 (b) (4) (b) (4)

S DRUG SUBSTANCE

BRIXADI™ (buprenorphine) extended release is a non-sterile API, and Microbiology review is not necessary.

Product Quality Microbiology Assessment

(0143/1.2/*cover-letter.pdf* & *cmc-reviewers-guide.pdf*)

The applicant has submitted this complete response, in response to one facility related deficiency. With the response to the CRL, the sponsor has also submitted some additional minor CMC updates and corrections/clarification to previously submitted data (b) (4) (b) (4) (b) (4) this is out of scope of Microbiology review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

While no changes are proposed for the drug product presentations, a brief description is included below for ease of review.

- **Description of drug product:** Unchanged. (b) (4) mL of a clear and colorless to pale yellow solution at a concentration of (b) (4) mg/mL (single use).
- **Drug product composition:** Unchanged

Composition of CAM2038 Drug Product

Component	Standard	Function	q1w Drug Product Composition/Dose (mg/mL)				q4w Drug Product Composition/Dose (mg/mL)			(b) (4)
			8/0.16	16/0.32	24/0.48	32/0.64	64/0.18	96/0.27	128/ 0.36	
Buprenorphine Base (BUP)	Ph. Eur.	API	8	16	24	32	64	96	128	
Ethanol Anhydrous (Dehydrated alcohol) (EtOH)	USP	(b) (4)							(b) (4)	
N-Methyl-2-Pyrrolidone (NMP)										
Soybean Phosphatidylcholine (SPC)	In-house									
Glycerol Dioleate (GDO)	In-house									
Total weight (mg) for all components/ dose	N/A	N/A								

*This is not an approved or to-be-marketed strength; however, this strength was used during development and process validation activities as part of a bracketing strategy.

- **Description of Container Closure System:** Unchanged; The CAM2038 q1w and CAM2038 q4w drug products are presented as pre-filled syringes (PFS). (b) (4)

(b) (4) syringes and (b) (4) plunger stoppers are the primary container closure.

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

(b) (4)

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P.5 CONTROL OF DRUG PRODUCT
P.5.1 SPECIFICATION- No changes proposed

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Package Insert – No changes proposed

MICROBIOLOGY LIST OF DEFICIENCIES- None

Primary Assessor Name and Date: Gouri Chattopadhyay, Ph. D., 03/21/2023
Secondary Assessor Name and Date: CAPT Paul Dexter, M.S., 03/21/2023

Gouri Chattopadhyay

Digitally signed by Gouri Chattopadhyay
Date: 3/22/2023 05:47:23PM
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Paul Dexter

Digitally signed by Paul Dexter
Date: 3/22/2023 01:22:58PM
GUID: 508da70c00028f8ef6fc7fb5f60df2ce

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 5/02/2023 09:52:05AM
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/s/

VALERIE R AMSPACHER
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 210136
Assessment 4

Drug Product Name	50 mg/mL buprenorphine q1w FluidCrystal subcutaneous injection depot 356 mg/mL buprenorphine q4w FluidCrystal subcutaneous injection depot
Dosage Form	subcutaneous injection depot
Strength	50 mg/mL buprenorphine (q1w - 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL) 356 mg/mL buprenorphine (q4w - 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL)
Route of Administration	subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Braeburn Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 129; eCTD 0128	15 Jun 21	Drug product, facilities
Supporting document 131; eCTD 0132	4 Oct 21	Drug product
Supporting document 133; eCTD 0133	21 Oct 21	Facilities
Supporting document 134; eCTD 0134	21 Oct 21	Facilities
Supporting document 136; eCTD 0136	4 Nov 21	Facilities
Supporting document 138; eCTD 0138	18 Nov 21	Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Lane Christensen	Yiwei Li
Microbiology	N/A	N/A
Biopharmaceutics	Hansong Chen	Okpo Eradiri
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The CMC recommendation is complete response for this application based on facilities review. An on-site inspection occurred and the facility remains to be "Official Action Indicated" based on the inspection. OPMA has issued a withhold recommendation. All other CMC disciplines recommend approval.

A shelf-life of 36 months is assigned to the drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Also see assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The CAM2038 50 mg/mL buprenorphine q1w and subcutaneous injection depot (hereinafter denoted CAM2038 q1w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once weekly dosing).

The CAM2038 q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine

(SPC)/ Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. Different drug product strengths, or doses, are accomplished by different syringe fill volumes.

The CAM2038 356 mg/mL buprenorphine q4w subcutaneous injection depot (hereinafter denoted CAM2038 q4w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once monthly dosing).

The CAM2038 q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 40/60 to final volume. Different drug product strengths, or doses, are accomplished by different syringe fill volumes.

In this resubmission the applicant provides new stability data and an updated dissolution method. The facilities will also be re-inspected.

The sponsor previously received a complete response letter on 19 Jan 2018. They received a tentative approval letter on 12 Dec 2018. A complete response letter was issued 1 Dec 2020 due to facility issues.

A shelf-life of 36 months is assigned to the drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Proposed Indication(s) including Intended Patient Population	Treatment of opioid use disorder (OUD) in adults
Duration of Treatment	chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Choose an item.

N/A
See also assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

Drug Product: Adequate

The sponsor provides additional stability data in this resubmission which supports a shelf-life of 36 months.

See also assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

Labeling: Adequate

See also assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

Manufacturing: Inadequate

While the process review remains adequate, facilities are NOT adequate.

During the previous review cycle, a PAI was performed in July 2020 for a separate application to be manufactured using (b) (4) and this PAI identified significant deficiencies (b) (4) Refer to (b) (4)

As a result of these deficiencies, the management of Pii voluntarily shut-down the facilities (both the vial and syringe manufacturing areas) in order to implement systematic corrective and preventive actions.
Consequently, it was decided to perform another PAI for this application in order to confirm the readiness and the capability of the firm to manufacture and to test Buprenorphine extended-release solution for injection in a pre-filled syringe.

A follow-up PAI was performed for NDA 210136 in October 2020 and based on the findings (refer to (b) (4) for the Expedited Review and to (b) (4) for the PAI Review); a withhold recommendation was made for existing drug product manufacturing facility ((b) (4) FEI 3006503102) and the existing principal facility for on-site drug product testing ((b) (4) FEI 1000513101) respectively.

As part of the evaluation during the current review cycle, a follow-up PAI was performed for NDA 210136 in August 2021 and based on the findings (refer to (b) (4) for the Expedited Review and to (b) (4) (b) (4) for the PAI Review); a withhold recommendation was made for existing drug product manufacturing facility ((b) (4) FEI 3006503102) and the existing principal facility for on-site drug product testing ((b) (4) FEI 1000513101) respectively.

See also assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

Biopharmaceutics: Adequate

Biopharm was adequate in the second review cycle. However, because their definitions of Leve 1 and Level 2 in vitro release (IVR) acceptance criteria were wrong, we requested the Applicant to follow USP <711> Table 2 for L1, L2, and L3 during the third review cycle.

In this resubmission, the Applicant reported that they retrospectively checked the stability data of registration and PPQ batches and found that some batches of monthly (q4w) formulation meet their originally proposed acceptance criteria, but failed to meet the approved criteria at some early time points (b) (4)

(b) (4)

From a Biopharmaceutics perspective, this Reviewer concludes that the failure of the monthly (q4w) stability samples is not significant because of the following reasons:
1)The failure mainly occurred at early time points, and those batches meet the approved acceptance criteria at subsequent time points.
2)The Applicant took effective measures (b) (4)

(b) (4)

See also assessment 3 facilities addendum dated 25 Nov 20, assessment 3 dated 9 Oct 20, assessment 2 dated 7 Dec 2018 and assessment 1 dated 26 Dec 2017.

Microbiology (if applicable): Choose an item.

N/A

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

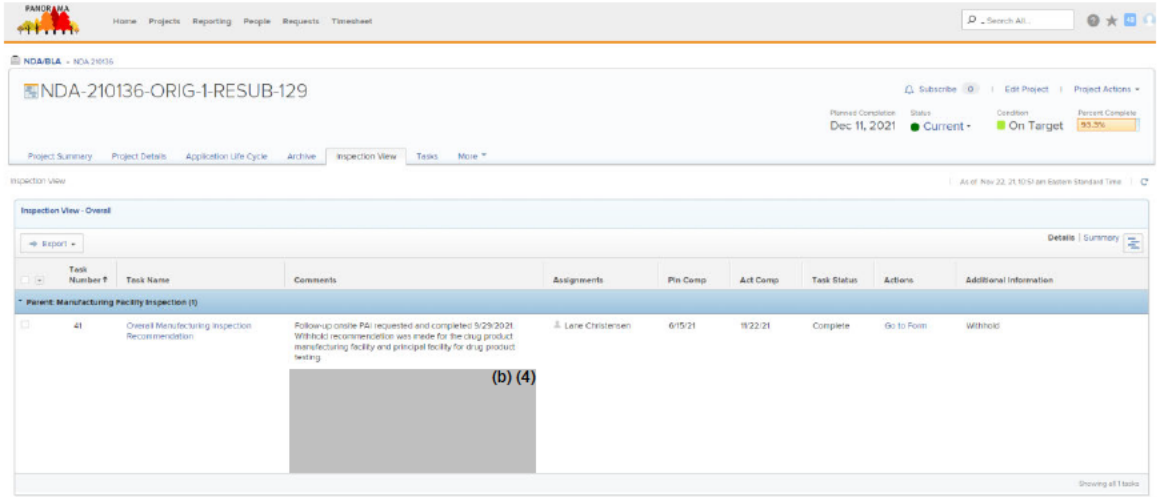
During a recent inspection for this application of the Pharmaceutics International (b) (4) (FEI 3006503102) manufacturing and testing facility located in Cockeysville, MD and the Pharmaceutics International (b) (4) (FEI 1000513101) warehouse and testing facility located in Hunt Valley, MD; our field investigator conveyed deficiencies to the representatives of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Inspection view screenshot showing withhold recommendation taken 22 Nov 2021



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BIOPHARMACEUTICS

NDA: NDA 210136-ORIG-1-RESUB-129 (4th cycle)

Drug Product Name / Strength: BRIXADI (buprenorphine) extended-release subcutaneous injection
8 mg, 16 mg, 24 mg, and 32 mg (once weekly administration)
64 mg, 96 mg, and 128 mg (once monthly administration)

Route of Administration: Subcutaneous injection

Applicant Name: Braeburn Pharmaceuticals, Inc.

A CR was issued to this NDA during last review cycle (3rd cycle) due to facilities issues.

Biopharm was adequate in the second review cycle. However, because their definitions of Leve 1 and Level 2 in vitro release (IVR) acceptance criteria were wrong, we requested the Applicant to follow USP <711> Table 2 for L1, L2, and L3 during the third review cycle.

In this resubmission, the Applicant reported that they retrospectively checked the stability data of registration and PPQ batches and found that some batches of monthly (q4w) formulation meet their originally proposed acceptance criteria, but failed to meet the approved criteria at some early time points (b) (4)

(b) (4)

From a Biopharmaceutics perspective, this Reviewer concludes that the failure of the monthly (q4w) stability samples is not significant because of the following reasons:

1) The failure mainly occurred at early time points, and those batches meet the approved acceptance criteria at subsequent time points.
2) The Applicant took effective measures (b) (4)

(b) (4)

Primary Biopharmaceutics Reviewer:

Hansong Chen, PharmD, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Secondary Reviewer:

Okpo Eradiri, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
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Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 10/22/2021 02:16:00PM
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Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 11/22/2021 01:48:10PM
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/s/

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 210136
Assessment 3 Facilities amendment

Drug Product Name	50 mg/mL buprenorphine q1w FluidCrystal subcutaneous injection depot 356 mg/mL buprenorphine q4w FluidCrystal subcutaneous injection depot
Dosage Form	subcutaneous injection depot
Strength	50 mg/mL buprenorphine (q1w - 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL) 356 mg/mL buprenorphine (q4w - 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL)
Route of Administration	subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Braeburn Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting Document 113; eCTD 0113	1 Jun 20	Resubmission, drug product, facilities
Supporting Document 116; eCTD 0116	24 Aug 20	Drug product
Supporting Document 118; eCTD 0118	16 Sep 20	Drug Product
Supporting Document 121; eCTD 0121	28 Sep 20	Drug Product
Supporting Document 123; eCTD 0123	6 Oct 20	Biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A

Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Frank Wackes	Joanne Wang
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The CMC recommendation is complete response for this application based on facilities review. An on-site inspection occurred and the facility was determined to be "Official Action Indicated" and OPMA has issued a withhold recommendation. All other CMC disciplines recommend approval.

A shelf-life of 24 months is assigned to the once weekly (q1w) drug product and a shelf-life of 36 months is assigned to the once monthly (q4w) drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Also see review #3 dated 9 Oct 20, review #2 dated 7 Dec 2018 and review #1 dated 26 Dec 2017.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The CAM2038 50 mg/mL buprenorphine q1w and subcutaneous injection depot (hereinafter denoted CAM2038 q1w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once weekly dosing).

The CAM2038 q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. Different drug product strengths, or doses, are accomplished by different

syringe fill volumes.

The CAM2038 356 mg/mL buprenorphine q4w subcutaneous injection depot (hereinafter denoted CAM2038 q4w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once monthly dosing).

The CAM2038 q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 40/60 to final volume. Different drug product strengths, or doses, are accomplished by different syringe fill volumes.

In this resubmission the applicant provides new stability data and proposes a change to dissolution specifications as well as (b) (4) (b) (4) specifications.
The previous review dated 7 Dec 2018 (review #2) recommended approval for this product. The facility required re-inspection during this review cycle (review #3) and was determined to be "Official Action Indicated" and OPMA has issued a withhold recommendation. The CMC recommendation at this time will be for complete response.

A shelf-life of 24 months is assigned to the once weekly (q1w) drug product and a shelf-life of 36 months is assigned to the once monthly (q4w) drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Proposed Indication(s) including Intended Patient Population	Treatment of opioid use disorder (OUD) in adults
Duration of Treatment	chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Choose an item.

N/A

Drug Product: Adequate

See review #3 dated 9 Oct 20, review #2 dated 7 Dec 2018 and review #1 dated 26 Dec 2017.

Labeling: Adequate

See review #3 dated 9 Oct 20, review #2 dated 7 Dec 2018 and review #1 dated 26 Dec 2017.

Manufacturing: Inadequate

During the current review cycle, a PAI was performed in July 2020 for a separate application to be manufactured using (b) (4) and this PAI identified significant deficiencies (b) (4) Refer to (b) (4)

As a result of these deficiencies, the management of Pii voluntarily shut-down the facilities (both the vial and syringe manufacturing areas) in order to implement systematic corrective and preventive actions. Consequently, it was decided to perform another PAI for this application in order to confirm the readiness and the capability of the firm to manufacture and to test Buprenorphine extended-release solution for injection in a pre-filled syringe.

A follow-up PAI was performed for NDA 210136 in October 2020 and based on the findings (refer to (b) (4) for the Expedited Review and to (b) (4) for the PAI Review); a withhold recommendation was made for existing drug product manufacturing facility ((b) (4) FEI 3006503102) and the existing principal facility for on-site drug product testing ((b) (4) FEI 1000513101) respectively.

Biopharmaceutics: Adequate

See review #3 dated 9 Oct 20, review #2 dated 7 Dec 2018 and review #1 dated 26 Dec 2017.

Microbiology (if applicable): Choose an item.

N/A

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

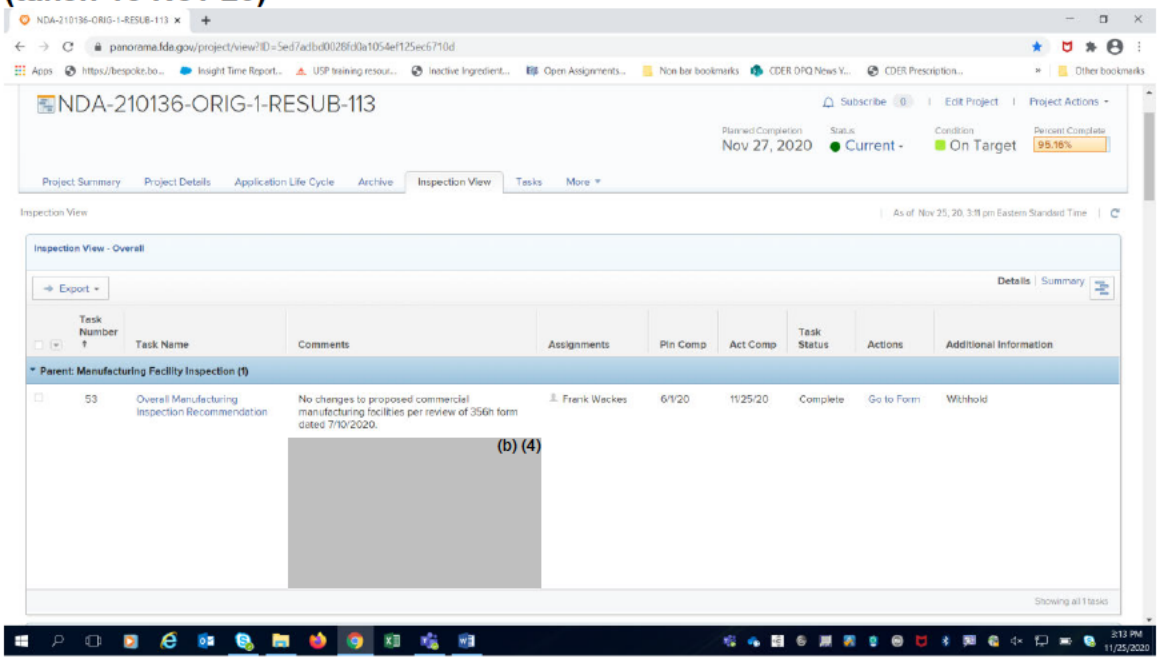
During a recent inspection for this application of the Pharmaceutics International (b) (4) (FEI 3006503102) manufacturing and testing facility located in Cockeysville, MD and the Pharmaceutics International (b) (4) (FEI 1000513101) warehouse and testing facility located in Hunt Valley, MD; our field investigator conveyed deficiencies to the representatives of each facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Inspection view screenshot showing withhold recommendation (taken 15 Nov 20)



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/s/

VALERIE R AMSPACHER
11/25/2020 03:39:01 PM

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 210136
Assessment 3

Drug Product Name	50 mg/mL buprenorphine q1w FluidCrystal subcutaneous injection depot 356 mg/mL buprenorphine q4w FluidCrystal subcutaneous injection depot
Dosage Form	subcutaneous injection depot
Strength	50 mg/mL buprenorphine (q1w - 8 mg/0.16 mL; 16 mg/0.32 mL; 24 mg/0.48 mL; 32 mg/0.64 mL) 356 mg/mL buprenorphine (q4w - 64 mg/0.18 mL; 96 mg/0.27 mL; 128 mg/0.36 mL)
Route of Administration	subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Braeburn Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting Document 113; eCTD 0113	1 Jun 20	Resubmission, drug product, facilities
Supporting Document 116; eCTD 0116	24 Aug 20	Drug product
Supporting Document 118; eCTD 0118	16 Sep 20	Drug Product
Supporting Document 121; eCTD 0121	28 Sep 20	Drug Product
Supporting Document 123; eCTD 0123	6 Oct 20	Biopharm

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A

Drug Product	Valerie Amspacher	Julia Pinto
Manufacturing	Frank Wackes	Joanne Wang
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

A CMC recommendation is pending facilities inspection and process review. Based on the review of the information provided in this resubmission drug product and biopharm recommends approval. Once the process and facility review is complete, an addendum with the final, overall CMC approvability recommendation will be added in Panorama and DARRTS.

Due to a need for facility re-inspection prior to re-opening this application will remain open and no CMC recommendation will be made until the on-site, in-person inspection can be completed.

A shelf-life of 24 months is assigned to the once weekly (q1w) drug product and a shelf-life of 36 months is assigned to the once monthly (q4w) drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Also see review #2 dated 7 Dec 2018 and review #1 dated 26 Dec 2017

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The CAM2038 50 mg/mL buprenorphine q1w and subcutaneous injection depot (hereinafter denoted CAM2038 q1w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once weekly dosing).

The CAM2038 q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. Different drug product strengths, or doses, are accomplished by different syringe fill volumes.

The CAM2038 356 mg/mL buprenorphine q4w subcutaneous injection depot (hereinafter denoted CAM2038 q4w) drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended release product (once monthly dosing).

The CAM2038 q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and Soybean Phosphatidylcholine (SPC)/ Glycerol Dioleate (GDO) in the weight ratio 40/60 to final volume. Different drug product strengths, or doses, are accomplished by different syringe fill volumes.

In this resubmission the applicant provides new stability data and proposes a change to dissolution specifications as well as (b) (4) (b) (4) specifications.
The previous review dated 7 Dec 2018 (review #2) recommended approval for this product. Due to a need for facility re-inspection prior to re-opening this application will remain open and no CMC recommendation will be made until the on-site, in-person inspection can be completed.

A shelf-life of 24 months is assigned to the once weekly (q1w) drug product and a shelf-life of 36 months is assigned to the once monthly (q4w) drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C.

Proposed Indication(s) including Intended Patient Population	Treatment of opioid use disorder (OUD) in adults
Duration of Treatment	chronic
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Choose an item.

N/A

Drug Product: Adequate

The sponsor requests [redacted] We do not agree to the change in specifications. The sponsor has agreed to use the specifications agreed to in review #2 dated 7 Dec 2018.

The sponsor updates the excipient analytical methods. [redacted]

The sponsor also tightened system suitability acceptance criteria. Due to changes in the handling of standards, the methods were revalidated. The methods remain suitable for use [redacted]

Labeling: Adequate

Manufacturing: Choose an item.

Pending

An inspection of the PHARMACEUTICS INTERNATIONAL, INC., FEI 1000513101 and 3006503102 facility is required before the application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP.

PAI was performed [redacted] at Pii (FEI 3006503102) and for Pii (FEI 1000513101). DP Facility was shut-down and re-inspection after start-up and completion of proposed corrective actions is pending.

Biopharmaceutics: Adequate

In this resubmission, the Applicant submitted additional IVR data to propose the following change in the acceptance criteria of Q4W:

Timepoints	Approved acceptance criteria in the previous review cyle	Newly proposed criteria
1 hr	NMT [redacted]	No Change
6 hr	[redacted]%	No Change

12 hr	(b) (4)%	(b) (4)%
72 hr	NLT (b) (4)%	No Change

The proposed change in the acceptance criteria at 12 hours for Q4W is acceptable. However, the Applicant's definition of Level 1 and Level 2 acceptance criteria is wrong. In the IR response, the Applicant agreed to implement the USP <711> acceptance criteria for both CAM2038 Q1W and Q4W formulations. In addition, the acceptance criterion at 72 hours' time point for Q4W was revised from "NLT (b) (4)%" to "NLT (b) (4)%" based on an agreement between FDA and the Applicant.

Overall, the following in vitro drug release acceptance criteria have been approved:

Strength	In vitro drug release acceptance criteria
8 mg, 16 mg, 24 mg, and 32 mg (Q1W)	**Level 1**: 6 hours: (b) (4)% released 48 hours: (b) (4)% released 168 hours: NLT (b) (4)% released **Level 2 and Level 3** Comply with USP <711>
64 mg, 96 mg, and 128 mg (Q4W)	**Level 1**: 1 hour: NMT (b) (4)% released 6 hours: (b) (4)% released 12 hours: (b) (4)% released 72 hours: NLT (b) (4) released **Level 2 and Level 3** Comply with USP <711>

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment – See Review 2 dated 7 Dec 2018

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
		H, M, or L		Acceptable or Not Acceptable	
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/ equipment	L	Controlled with specifications	Acceptable	

	• Site				
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled with specifications	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	Controlled with specifications	Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/ equipment	L	Controlled with specifications	Acceptable	
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	Controlled with specifications	Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	1	6 Nov 2017	
	IV			1	30 Nov 2018	(b) (4)
	IV			1	6 Dec 2017	
	III			4		Reviewed by micro
	III			4		Used in approved products. Will use (b) (4) information provided by this application.
	V			4		Reviewed by micro

(b) (4)	III	(b) (4)	4		Used in approved products. Will use (b) (4) information provided by this application.

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	114082	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Valerie Amspacher

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Assessment: N/A

Post-Approval Commitments

Assessment: N/A

Lifecycle Management Considerations

DRUG PRODUCT LIST OF DEFICIENCIES

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate.

This application is recommended for approval per labeling/labels perspective once following changes listed in the tables below have been made to the label.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	"extended-release injection" is listed n the product title guidance
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose is used correctly in other sections	Single dose is used correctly in other sections

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	Not a salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	Need to add "sterile, yellowish to yellow clear liquid"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single dose is used correctly in this section	Single dose is used correctly in this section

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	"extended-release injection" is listed in the product title guidance
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	% is for OTC, need to list mg/mL	% is for OTC, need to list mg/mL Per email from David Claffey dated 2 Sep 20 the amount of alcohol present must be specified clearly
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single dose is correctly used here	Single dose is correctly used here

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Yes	Contains a latex caution statement in most other sections
Include information about child-resistant packaging		

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

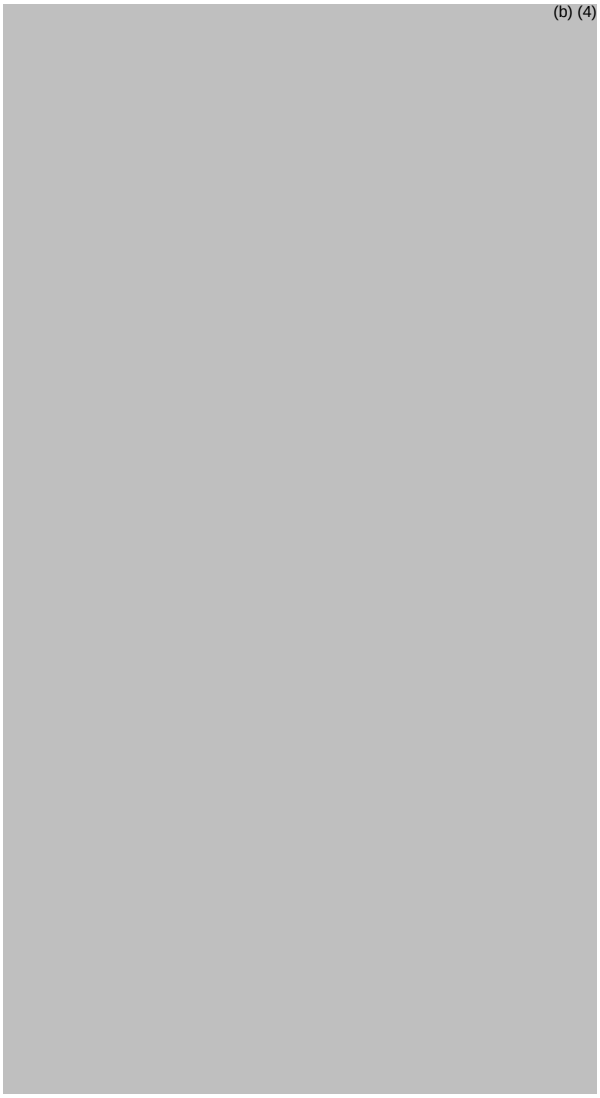
Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
Adequate. The PI complies with all statutory/regulatory requirements and is consistent with guidance recommendations from a product quality perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

These are the labels that will be on individual syringes
Only 1 example of the 4 once weekly doses available and 1 example of the 3 once monthly doses available will be included here

Once weekly



3.2 Carton Labeling

Only 1 example of the 4 once weekly doses available and 1 example of the 3 once monthly doses available will be included here

Once Weekly

(b) (4)

Once monthly

(b) (4)

Item	Container (syringe) label 8 mg/ 16 mg/ 24 mg/ 32 mg/ 64 mg/ 96 mg/ 128 mg	Carton Labeling 8 mg/ 16 mg/ 24 mg/ 32 mg/ 64 mg/ 96 mg/ 128 mg
Proprietary name, established name, and dosage form (font size and prominence	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
Dosage strength	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
Route of administration	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
"Rx only" displayed on the principal display	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
NDC number	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
Lot number and expiration date	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	On carton labeling	Y/Y/Y/Y/Y/Y/Y
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	No, did we already decide this isn't needed on the packaging	No, did we already decide this isn't needed on the packaging
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	% is for OTC, need to list mg/mL	% is for OTC, need to list mg/mL Per email from David Claffey dated 2 Sep 20 the amount of alcohol present must be specified clearly

Bar code	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Y/Y/Y/Y/Y/Y/Y	Y/Y/Y/Y/Y/Y/Y
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: Adequate.
Immediate container label(s) comply with all statutory/regulatory requirements and are consistent with guidance recommendations from a Quality perspective.

Valerie Amspacher

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Julia Pinto

Digitally signed by Julia Pinto
Date: 10/07/2020 12:51:18PM
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BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background: NDA 210136 for BRIXADI (buprenorphine) extended-release subcutaneous injection was tentatively approved on Dec 21, 2018 due to regulatory exclusivity for Sublocade (NDA209819), which will expire on Nov 30, 2020. The Applicant submitted this amendment to request a final approval of NDA 210136. The proposed drug product is indicated for opioid use disorder (OUD) (b) (4) (b) (4)

NDA: NDA 210136-ORIG-1-RESUB-113

Drug Product Name / Strength: BRIXADI (buprenorphine) extended-release subcutaneous injection
8 mg, 16 mg, 24 mg, and 32 mg (once weekly administration)
64 mg, 96 mg, and 128 mg (once monthly administration)

Route of Administration: Subcutaneous injection

Applicant Name: Braeburn Pharmaceuticals, Inc.

Review Recommendation: **Adequate**

Review Summary:
In the last review cycle, the following in vitro release (IVR) acceptance criteria have been approved:

Strength	In vitro release acceptance criteria
8 mg, 16 mg, 24 mg, and 32 mg (Q1W)	**Level 1:** (b) (4) 6 hours: (b) (4) % released 48 hours: (b) (4) % released 168 hours: NLT (b) (4) % released **Level 2:** (b) (4)
64 mg, 96 mg, and 128 mg (Q4W)	**Level 1:** (b) (4) 1 hour: NMT (b) (4) % released

	6 hours: (b) (4)% released 12 hours: (b) (4)% released 72 hours: NLT (b) (4)% released **Level 2:** The same conditions previously proposed as Q1W

In this resubmission, the Applicant submitted additional IVR data to propose the following change in the acceptance criteria of Q4W:

Time points	Approved acceptance criteria in the review cycle	Newly proposed criteria
1 h	NMT (b) (4)%	No change
6 h	(b) (4)%	No change
12 h	(b) (4)%	(b) (4)%
72 h	NLT (b) (4)%	No change

The proposed change in the acceptance criteria at 12 hours for Q4W is acceptable. However, the Applicant's definition of Level 1 and Level 2 acceptance criteria is wrong. In the IR response, the Applicant agreed to implement the USP <711> acceptance criteria for both CAM2038 Q1W and Q4W formulations. In addition, the acceptance criterion at 72 hours' time point for Q4W was revised from "NLT (b) (4)%" to "NLT (b) (4)%" based on an agreement between FDA and the Applicant.

Overall, the following in vitro drug release acceptance criteria have been approved:

Strength	In vitro drug release acceptance criteria
8 mg, 16 mg, 24 mg, and 32 mg (Q1W)	**Level 1:** 6 hours: (b) (4)% released 48 hours: (b) (4)% released 168 hours: NLT (b) (4)% released **Level 2 and Level 3** Comply with USP <711>
64 mg, 96 mg, and 128 mg (Q4W)	**Level 1:** 1 hour: NMT (b) (4) released 6 hours: (b) (4)% released 12 hours: (b) (4)% released 72 hours: NLT (b) (4)% released **Level 2 and Level 3** Comply with USP <711>

Conclusion:
From a biopharmaceutics perspective, this Reviewer recommends that NDA 210136-ORIG-1-RESUB-113 for BRIXADI (buprenorphine) extended-release subcutaneous injection is adequate for approval.

List Submissions being reviewed (table):

June 1, 2020	CTD 0104- Resubmission
October 6, 2020	CTD 0123- Response to the Biopharm IR

Highlighted Key Outstanding Issues from Last Cycle: None.

Concise Description of Outstanding Issues Remaining: None.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate}***

1. Approved in vitro release (IVR) method

In previous review cycles, the following in vitro drug release method have been approved:

Apparatus	Apparatus 1 (basket)
Rotation speed	50 rpm
Medium and Volume	Q1W: Citric acid buffer, 100 mM, pH 3.0, 900 mL Q4W: Citric acid buffer, 100 mM, pH 4.0, 500 mL
Temperature	37 ± 0.5 °C

To reduce IVR variability, the Applicant improved the in vitro release method in the following:

(b) (4)

(b) (4)

2. Proposed change in this resubmission and supporting data

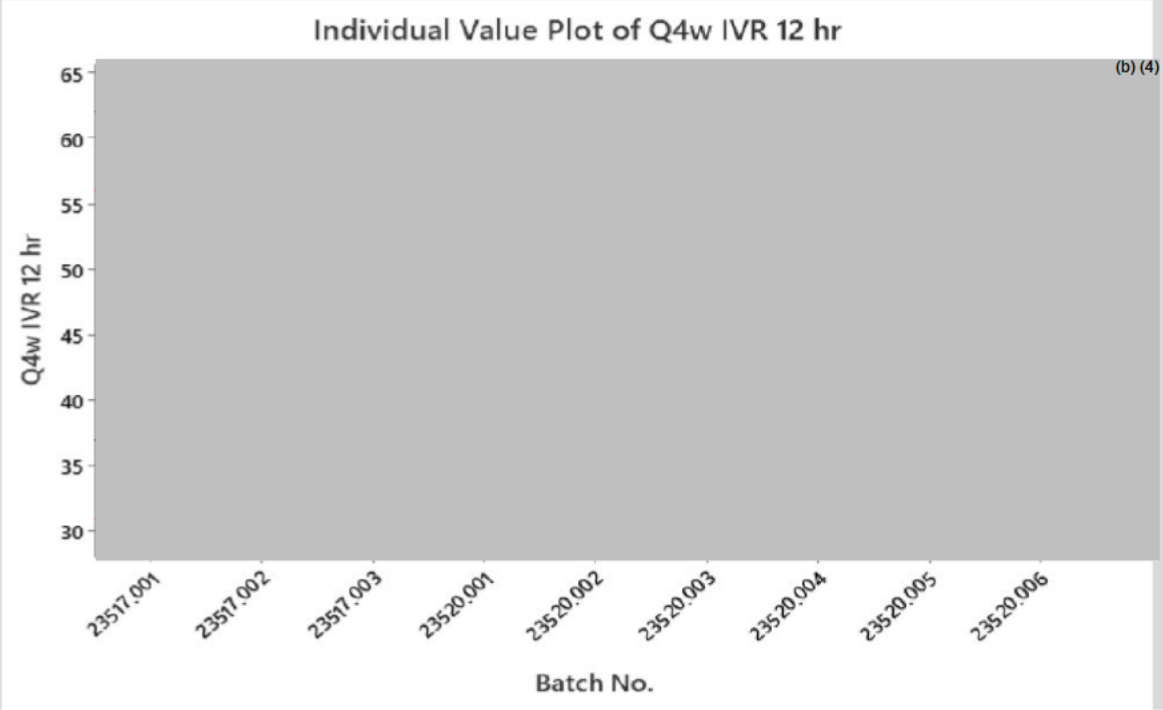
In this resubmission, the Applicant provided additional IVR data to request a change the approved acceptance criterion at 12 hours for Q4W from (b) (4)% to (b) (4)%. The detailed proposed change in acceptance criteria is listed below:

Time points	Approved acceptance criteria in the review cycle	Newly proposed criteria
1 h	NMT (b) (4)%	No change
6 h	(b) (4)%	No change
12 h	(b) (4)%	(b) (4)%
72 h	NLT (b) (4)%	No change

In vitro drug release data at 12 hours

Per the Applicant, the original IVR acceptance criteria were proposed and approved based on limited IVR data (n=25). The newly stability data show (b) (4) (b) (4) In this resubmission, the Applicant provided more IVR data (n=98) including release and stability generated on registration, PPQ, and annual batches (b) (4) (b) (4) (b) (4)

Figure 1. Individual Data Plots for CAM2038 Q4W – IVR 12-hr Timepoint (n=98)



The Applicant summarized all individual IVR data at 12 hours shown in Figure 1, which indicates (b) (4) in vitro release between (b) (4)%. Therefore, they proposed to change the acceptance criteria at 12 hours for Q4W from (b) (4)% to (b) (4)%.

In vitro drug release data at 72 hours

In this resubmission, the Applicant also summarized IVR data at 72 hours based on 98 individual units, as shown in Figure 2.

Figure 2. 72-hour IVR data from Clinical, Stability, PPQ and Annual lots by Compounding Batch

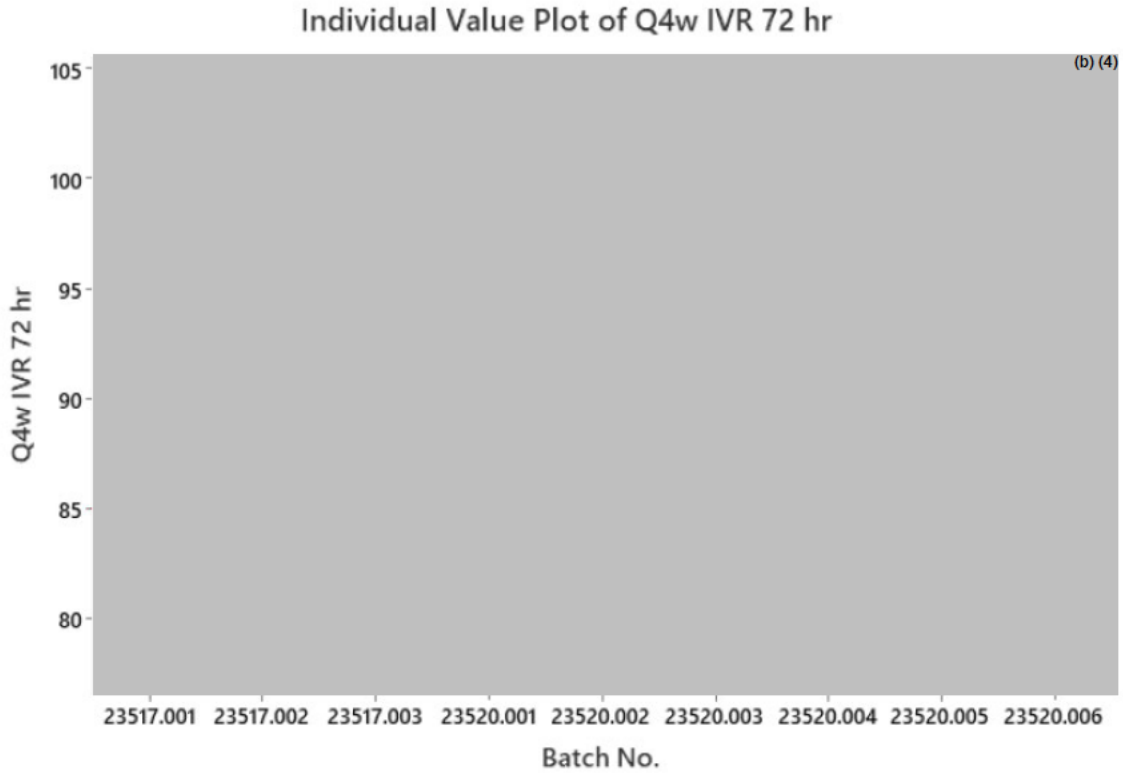


Figure 2 shows that the 72-hour data range (b) (4)
(b) (4)
(b) (4)
respectively.
The Applicant investigated IVR variability and found that the root cause is (b) (4)
(b) (4) Therefore, the Applicant implemented the above method improvements to ensure consistent results for the 72-hour timepoint and other time points.

Reviewer's comment

The proposed change in the acceptance criteria at 12 hours for Q4W is acceptable. However, the Applicant's definition of Level 1 and Level 2 acceptance criteria is wrong and not acceptable. Specifically, their proposed Level 1 and Level 2 acceptance criteria are extremely permissive and have no value for the quality control of their drug product at all.

Acceptance criteria for extended-release drug products should conform to Acceptance Table 2 of USP <711>. Therefore, the Applicant were requested to comply with USP <711> Level 1 and Level 2 definitions and implement the following IVR acceptance criteria for their approved drug product:

Strength	*In vitro drug release acceptance criteria*
8 mg, 16 mg, 24 mg, and 32 mg (Q1W)	***Level 1:*** *6 hours: (b) (4) % released* *48 hours: (b) (4) % released* *168 hours: NLT (b) (4) % released* ***Level 2 and Level 3*** *Comply with USP <711>*
64 mg, 96 mg, and 128 mg (Q4W)	***Level 1:*** *1 hour: NMT (b) (4) % released* *6 hours: (b) (4) % released* *12 hours: (b) (4) % released* *72 hours: NLT (b) (4) % released* ***Level 2 and Level 3*** *Comply with USP <711>*

The individual IVR data provided in this resubmission show that their drug product (both Q1W and Q4W) is able to meet the above acceptance criteria.

In the response to the Biopharm IR, the Applicant agreed to implement the USP <711> acceptance criteria for both CAM2038 Q1W and Q4W formulations, except the 72 hr timepoint for Q4W. To meet the requirements of USP <711> for the 72 hr timepoint, they proposed to change the acceptance criterion from NLT (b) (4) % to NLT (b) (4) %. Based on the individual IVR data of Q4W, this Reviewer concludes that the newly proposed change in 72 hours acceptance criterion of Q4W is acceptable.

Appendix

Biopharmaceutics Information Request and Applicant's Response

IR

Your proposed change in the in vitro drug release acceptance range at 12 hours for Q4W is acceptable. However, note that your definitions of Level 1 and Level 2 acceptance criteria are wrong.

Refer to USP<711>, table 2, for in vitro drug release acceptance criteria for extended-release drug products, including definitions of Levels 1, 2, and 3. We recommend that you include the USP definitions, without edits, in the specifications table of the Application.

The approved in vitro drug release acceptance criteria for your approved drug products are:

Strength	In vitro drug release acceptance criteria
8 mg, 16 mg, 24 mg, and 32 mg (Q1W)	**Level 1:** 6 hours: (b) (4)% released 48 hours: (b) (4)% released 168 hours: NLT (b) (4)% released **Level 2 and Level 3** Comply with USP <711>
64 mg, 96 mg, and 128 mg (Q4W)	**Level 1:** 1 hour: NMT (b) (4)% released 6 hours: (b) (4)% released 12 hours: (b) (4)% released 72 hours: NLT (b) (4)% released **Level 2 and Level 3** Comply with USP <711>

Implement the above dissolution acceptance criteria for your drug product and update the drug product specification tables and other relevant parts of your NDA accordingly. If you need additional clarification, please send a request to the Regulatory Project Manager for a teleconference.

The Applicant's response:

After a thorough review of the raw data, Braeburn agrees to implement the USP <711> acceptance criteria for the CAM2038 Q1W formulation. For the Q4W formulation, Braeburn agrees to implement the USP <711> acceptance criteria for all timepoints, except for the 72 hr timepoint. When the 12 and 72 hr timepoints were added to the release and stability specification for the Q4W formulation, our acceptance criteria (e.g. the mean) were used to set the proposed specification limits. To meet the requirements of USP <711> for the 72 hr timepoint, Braeburn is proposing to change the acceptance criteria from NLT (b) (4)% to NLT (b) (4)%, which is in alignment with Section VII.B.1 of FDA

Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations.

Reviewer's comment:

The response is adequate.

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***{Adequate/Inadequate}***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer:

Hansong Chen, PharmD, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Secondary Reviewer:

Okpo Eradiri, Ph.D.
Division of Biopharmaceutics/ONDP/OPQ

Hansong Chen

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Valerie Amspacher

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Date: 10/09/2020 11:14:52AM
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/s/

VALERIE R AMSPACHER
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Executive Summary

Review #2

I. Recommendations and Conclusion on Approvability

Based on recommendations from facilities, CDRH-OC, microbiology, biopharmaceutics, and drug product, CMC recommends approval of CAM2038 q1w 8 mg/0.16 mL, CAM2038 q1w 16 mg/0.32 mL, CAM2038 q1w 24 mg/ 0.48 mL, CAM2038 q1w 32 mg/0.64 mL, CAM2038 q4w 64 mg/0.18mL, CAM2038 q4w 96 mg/0.27 mL, CAM2038 q4w 128 mg/ 0.36 mL (b) (4) (b) (4) In Review #1 drug substance and process recommended approval.

The stability data submitted supports a shelf-life of 24 months for the CAM2038 q1w and CAM2038 q4w drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C in the commercial container/closure system.

The following groups had deficiencies in the last cycle: Facilities (Office of Process and Facilities), CDRH-OC, Microbiology and Drug Product. All deficiencies have been resolved. See the body of this document for details.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	CAM2038 drug products have been developed as (b) (4) extended release buprenorphine products indicated for the treatment of opioid use disorder with CAM2038 q1w targeted for once weekly administration and CAM2038 q4w targeted for once monthly administration.
Duration of Treatment	Once weekly to once monthly
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

This is review cycle #2. This product received a complete response during the first review cycle. The sponsor has addressed all deficiencies in this review cycle. Deficiencies from review cycle #1 are listed below.

CAM2038 (buprenorphine) Injection, q1w and q4w, subcutaneous depot drug product is a liquid formulation that contains buprenorphine base, (b) (4) (b) (4) The CMC information for the drug substance buprenorphine base which is manufactured by (b) (4) is referenced in DMF# (b) (4) A letter of authorization was provided for the DMF and it was last reviewed and found adequate on 11/6/2017 by Dr. Erika Englund the reviewer of the NDA during the first review cycle. Buprenorphine base is a white or almost white crystalline powder with a melting point range between 216-218°C. It is freely soluble in water and (b) (4) (b) (4) that was observed. The drug substance has a retest period of (b) (4) months (b) (4)

CAM2038 is available as a once weekly and once monthly extended-release solution for injection in a pre-filled syringe available in CAM2038 q1w 8 mg/0.16 mL, CAM2038 q1w 16 mg/0.32 mL, CAM2038 q1w 24 mg/ 0.48 mL, CAM2038 q1w 32 mg/0.64 mL, CAM2038 q4w 64 mg/0.18mL, CAM2038 q4w 96 mg/0.27 mL, CAM2038 q4w 128 mg/ 0.36 mL (b) (4) strengths. The CAM2038 FluidCrystal subcutaneous injection depot drug product is a yellowish to yellow clear liquid which is (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. The drug product (b) (4)

The CAM2038 q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. According to the applicant, (b) (4) (b) (4) CAM2038 q1w and CAM2038 q4w drug product.

The stability data submitted supports a shelf-life of 24 months for the CAM2038 q1w and CAM2038 q4w drug product when stored at controlled room temperature, 25°C with excursions permitted from 15°C to 30°C in the commercial container/closure system.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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 • Process parameters • Scale/equipment • Site	L	-	N/A	-
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	N/A	-
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	N/A	-

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

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	1	6 Nov 2017	
	IV			1	30 Nov 2018	(b) (4)
	IV			1	6 Dec 2017	
	III			4		Reviewed by micro
	III			4		Used in approved products. Will use (b) (4) information provided by this application.
	V			4		Reviewed by micro
	III			4		Used in approved products. Will use (b) (4) information provided by this application.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

CDRH	Complete	Adequate	19 Jul 2018	Arabella Pelina

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	**Soumya Mitra**	**Donna Christner**
Drug Product	**Valerie Amspacher**	**Julia Pinto**
Process	**Pei-I Chu**	**Ubrani Venkataram**
Microbiology	**Koushik Paul**	**Elizabeth Bearr**
Facility	**Frank Wackes**	**Ying Zhang**
Biopharmaceutics	**Kelly Kitchens**	**Okpo Eradiri**
Regulatory Business Process Manager	**Steven Kinsley**	
Application Technical Lead	**Valerie Amspacher**	
Laboratory (OTR)	**N/A**	
ORA Lead	**Kelly Anderson/Alice Tsao**	
CDRH-OC	**Arabella Pelina**	**Maria Isabel Tejero Del Rio**

Valerie Amspacher

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Julia Pinto

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BIOPHARMACEUTICS

Product Background: Pursuant to 505(b)(2) pathway, the applicant submits an NDA for CAM2038 (buprenorphine extended-release), a subcutaneous injection intended for opioid use disorder (OUD) (b) (4) CAM2038 should be used as part of a complete treatment plan to include counseling and psychosocial support. The clinical study program was designed to evaluate efficacy across treatment phases (initiation, stabilization, and maintenance) and including both treatment-seeking adults with OUD, and patients transferred from treatment with daily sublingual (SL) buprenorphine (BPN) and transmucosal BPN/naloxone (NX) products. This NDA received priority review during the original submission since the product virtually eliminates the potential for abuse because it is administered by clinicians only and never dispensed to patients. CAM2038 is available as a Once Weekly and Once Monthly extended-release solution for injection in a pre-filled syringe.

NDA: 210136

Drug Product Name: Brixadi/CAM2038 (buprenorphine extended-release) subcutaneous injection

Strengths: 8 mg, 16 mg, 24 mg, and 32 mg (once weekly administration)
64 mg, 96 mg, and 128 mg (once monthly administration)

Reviewer's Note: In the original submission (July 19, 2017), the applicant (b) (4) (b) (4) In the May 23, 2018 resubmission, the applicant withdrew (b) (4) (b) (4) (see Module 1.11.3 for details).

Route of Administration: Subcutaneous Injection

Applicant Name: Braeburn Pharmaceuticals, Inc.

Review Recommendation: ADEQUATE

List Submissions being reviewed:

May 23, 2018	SN 0079/Resubmission
October 4, 2018	SN 0089/Response to FDA Request for Information: CMC
October 22, 2018	SN 0090/Response to FDA Request for Information: CMC

Review Summary:
The following Biopharmaceutics information were previously considered adequate (see the Biopharmaceutics review by Dr. An-Chi Lu in Panorama dated December 21, 2017):

- In vitro release method
  Apparatus: Apparatus 1 (basket)

Speed: 50 rpm at temperature 37°C ± 0.5°C
Medium for CAM2038 Q1W: Citric acid buffer, 100 mM, pH 3.0, 900 mL
Medium for CAM2038 Q4W: Citric acid buffer, 100 mM, pH 4.0, 500 mL

- In vitro release acceptance criteria for CAM2038 Q1W:

Level 1:

(b) (4)

6 hours: (b) (4)% released
48 hours: (b) (4)% released
168 hours: NLT (b) (4)% released

Level 2:

(b) (4)

- ***Interim*** in vitro release acceptance criteria for CAM2038 Q4W:

Level 1:

(b) (4)

1 hour: NMT (b) (4)% released
6 hours: (b) (4)% released
24 hours: (b) (4)% released
48 hours: NLT (b) (4)% released

Level 2:

(b) (4)

- Extended-Release claim.

In the resubmission, the applicant proposed the following revised in vitro release acceptance criteria for CAM2038 Q4W:

Level 1:

(b) (4)

1 hour: NMT (b) (4)% released
6 hours: (b) (4)% released
12 hours: (b) (4)% released
72 hours: NLT (b) (4)% released

Level 2: same conditions previously proposed

The revised in vitro release acceptance criteria for Q4W are adequate.

In addition, the applicant proposed (b) (4) (b) (4) as new release and stability testing sites for the finished product. Comparative in vitro release testing for batches manufactured at (b) (4) and Pii (Hunt Valley, MD), the previous testing facility, was conducted to support the addition of (b) (4) The comparative in vitro release testing supports the addition of the (b) (4) site.

In Vitro Release Acceptance Criteria

Reviewer's Assessment: Adequate

The following acceptance criteria were previously considered adequate for Q1W:
6 hours: (b) (4)% released
48 hours: (b) (4)% released
168 hours: NLT (b) (4)% released

The following acceptance criteria were previously considered adequate for Q4W on an interim basis, and the applicant agreed to update the acceptance criteria after generating additional data at the 12-hour and 72-hour timepoints:
1 hour: NMT (b) (4)% released
6 hours: (b) (4)% released
24 hours: (b) (4)% released
48 hours: NLT (b) (4)% released

The applicant proposed the following revised acceptance criteria in the resubmission:
1 hour: NMT (b) (4)% released
6 hours: (b) (4)% released
12 hours: (b) (4)% released
72 hours: NLT (b) (4)% released

The applicant proposed the 12-hour time point to replace the 24-hour time point (b) (4) (b) (4) (b) (4) In addition, data was generated at the 72-hour time point (b) (4) therefore, the applicant proposed to replace the 48-hour time point with the 72-hour time point. The following figure, generated from mean of mean in vitro release data, were used to support the proposed acceptance criteria:

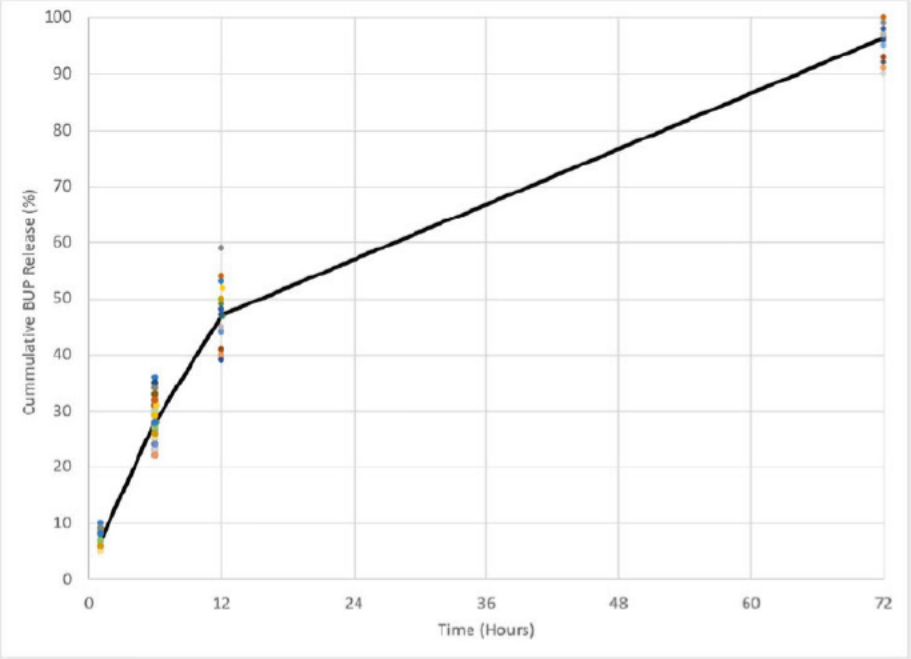

Figure 1. Dissolution data for CAM2038 q4w (mean values) obtained for clinical Phase III and formal stability batches at release and upon stability. The data are also tabulated in Table 6 (mean values). The fully drawn line represents the overall mean ("Mean of means", n = 77 for 1h and 6h, n=25 for 12h and 72h).

In an Information Request (IR) dated September 17, 2018, the complete in vitro release data (individual, mean, range, %RSD) were requested for the batches [pivotal clinical, formal stability, process performance quality (PPQ), and orientation] being used to support the proposed Q4W acceptance criteria. The applicant submitted the following IR response on October 4, 2018:

The complete in vitro release (IVR) data, including the individuals, mean, range, %RSD and date and method of testing for each time point are included in the attached spreadsheet titled ***CAM2038 – Complete IVR Data – Q1W and Q4W*** **(Reviewer's note:** refer to Excel file submitted in Module 3.2.P.5.6 Justification of Specifications). *There are two separate data sheets, one for Q1W and one for Q4W. For each release or stability timepoint, all IVR data generated, including those intervals which are not part of the proposed specification, are provided to show a complete profile.*

Section 3.2.P.5.4 Batch Analysis contains the detailed information for each of the batches tested which includes batch number, manufacturing date, purpose and batch size. Please refer to Table 1 for Q1W and Table 2 for Q4W for links to the batch details for each individual batch.

Table 1: Batch Information for Lots Used to Set the IVR Specification for CAM2038 Q1W Drug Product

Strength/Fill Vol.	Batch No.	Purpose	Link to Batch Info. in 3.2.P.5.4 – Q1W
8 mg/0.16 mL	23505.002	Clin. Ph3	Table 3
8 mg/0.16 mL	23505.003	Clin. Ph3	Table 3
8 mg/0.16 mL	23505.004	Clin. Ph3	Table 3
8 mg/0.16 mL	23505.007	Formal stability	Table 2
8 mg/0.16 mL	23505.008	Formal stability	Table 2
8 mg/0.16 mL	23505.009	Formal stability	Table 2
8 mg/0.16 mL	23505.010	PPQ	Table 15
8 mg/0.16 mL	23505.011	PPQ / Orientation	Table 15
16 mg/0.32 mL	23514.001	Clin. Ph3	Table 4
16 mg/0.32 mL	23514.002	Clin. Ph3 / Formal stability	Table 4
16 mg/0.32 mL	23514.005	Formal stability	Table 4
16 mg/0.32 mL	23514.006	Formal stability	Table 4
16 mg/0.32 mL	23514.007	PPQ	Table 15
24 mg/0.48 mL	23516.001	Clin. Ph3	Table 5
24 mg/0.48 mL	23516.002	Clin. Ph3	Table 5
24 mg/0.48 mL	23516.004	PPQ	Table 16
32 mg/0.64 mL	23506.003	Clin. Ph3 / Formal stability	Table 6
32 mg/0.64 mL	23506.004	Clin. Ph3 / Formal stability	Table 6
32 mg/0.64 mL	23506.002	Clin. Ph3	Table 7
32 mg/0.64 mL	23506.005	Formal stability	Table 6
32 mg/0.64 mL	23506.006	PPQ	Table 16
32 mg/0.64 mL	23506.007	PPQ / Orientation	Table 16

Table 2: Batch Information for Lots Used to Set the IVR Specification for CAM2038 Q4W Drug Product

Strength/Fill Vol.	Batch No.	Purpose	Link to Batch Info. in 3.2.P.5.4 – Q4W
64 mg/0.18 mL	23518.001	Clin. Ph3 / Formal stability	Table 2
64 mg/0.18 mL	23518.002	Clin. Ph3 / Formal stability	Table 2
64 mg/0.18 mL	23518.003	Clin. Ph3 / Formal stability	Table 2
64 mg/0.18 mL	23518.004	PPQ	Table 11
64 mg/0.18 mL	23518.005	PPQ / Orientation	Table 11
96 mg/0.27 mL	23519.001	Clin. Ph3	Table 3
96 mg/0.27 mL	23519.002	Clin. Ph3	Table 3
96 mg/0.27 mL	23519.003	PPQ	Table 11
128 mg/0.36 mL	23521.001	Clin. Ph3	Table 4
128 mg/0.36 mL	23521.002	Clin. Ph3	Table 4
128 mg/0.36 mL	23521.003	PPQ	Table 12
160 mg/0.45 mL	23522.001	Clin. Ph3 / Formal stability	Table 5
160 mg/0.45 mL	23522.002	Clin. Ph3 / Formal stability	Table 5
160 mg/0.45 mL	23522.003	Clin. Ph3 / Formal stability	Table 5
160 mg/0.45 mL	23522.004	PPQ / Orientation	Table 12
160 mg/0.45 mL	23522.005	PPQ	Table 12

Reviewer's note: in vitro release data for the 160 mg strength were not evaluated for the in vitro release acceptance criteria since this strength was withdrawn from the application.

The complete in vitro release data confirm the approved acceptance criteria for Q1W, and support the revised acceptance criteria for Q4W.

Addition of New Release and Stability Testing Site:

Reviewer's Assessment: Adequate

Prior to the Pii inspection in November 2017, the applicant sought (b) (4) with the intent to qualify (b) (4) as an alternative release and stability testing site. Both (b) (4) were qualified as alternative testing sites.

(b) (4)

Comparative in vitro release data were generated by Pii and (b) (4) for the lowest and highest strengths of PPQ batches.

In an IR dated October 17, 2018, the complete in vitro release data (individual, mean, range, %RSD) was requested for the batches used in comparative in vitro release testing to support the addition of the (b) (4) site. The applicant submitted the following IR response on October 22, 2018:

*The requested IVR data generated (b) (4) have been added to the previously submitted Excel file titled **CAM2038 - Complete IVR Data – Q1W and Q4W**, which included the data generated at Pii. The table below lists the row numbers within the Excel file to locate the comparative IVR dataset.*

Batch No.	Formulation	Strength	Pii – IVR Data (Excel Row Number)	(b) (4) IVR Data (Excel Row Number)
23505.010	Q1W	8 mg/0.16 mL	709 thru 722	723 thru 729
23506.007	Q1W	32 mg/0.64 mL	786 thru 799	800 thru 806
23518.004	Q4W	64 mg/0.18 mL	401 thru 414	415 thru 421
23521.003	Q4W	128 mg/0.36 mL	478 thru 491	492 thru 498

These data were used to calculate the similarity factor (f2) between batches tested at the Pii and (b) (4) sites.

CAM2038 Q1W, 8 mg/0.16 mL, batch 23505.010

Test parameter	Acceptance criteria	Pii		(b) (4)
	(b) (4)	Set 1	Set 2	Set 1
In vitro release[1] (% of LC)	Released at 6 hours: (b) (4) %	26	22	22
	Released at 48 hours: (b) (4) %	59	56	59
	Released at 168 hours: NLT (b) (4) %	88	84	88

F2 Metrics	(b) (4)
Pii (set 1)	75.8
Pii (set 2)	80.0

CAM2038 Q1W, 32 mg/0.64 mL, batch 23506.007

Test parameter	Acceptance criteria	Pii		(b) (4)
	(b) (4)	Set 1	Set 2	Set 1
In vitro release[1] (% of LC)	Released at 6 hours: (b) (4) %	22	20	21
	Released at 48 hours: (b) (4) %	57	53	55
	Released at 168 hours: NLT (b) (4) %	86	84	85

F2 Metrics	(b) (4)
Pii (set 1)	88.1
Pii (set 2)	88.1

CAM2038 Q4W, 64 mg/0.18 mL, batch 23518.004

Test parameter	Acceptance criteria	Pii		(b) (4)
	(b) (4)	Set 1	Set 2	Set 1
In vitro release[1] (% of LC)	Released at 1 hours: NMT (b) (4) %	8	7	7
	Released at 6 hours: (b) (4) %	29	27	25
	Released at 12 hours: (b) (4) %	54	48	42
	Released at 72 hours: NLT (b) (4) %	98	97	100

F2 Metrics	(b) (4)
Pii (set 1)	59.4
Pii (set 2)	71.9

CAM2038 Q4W, 128 mg/0.36 mL, batch 23521.003

Test parameter	Acceptance criteria	Pii		(b) (4)
	(b) (4)	Set 1	Set 2	Set 1
In vitro release[1] (% of LC)	Released at 1 hours: NMT (b) (4)%	6	7	8
	Released at 6 hours: (b) (4)%	22	26	28
	Released at 12 hours: (b) (4)%	40	45	47
	Released at 72 hours: NLT (b) (4)%	91	97	94

F2 Metrics	(b) (4)
Pii (set 1)	64.8
Pii (set 2)	81.5

Table footnotes:

1. For Pii's testing, two sets of n=6 are provided for each PPQ batch at release due to the more extensive sampling requirements of this study.

(b) (4)

The similarity f2 metrics are greater than 50, indicating the in vitro release profiles for batches tested at Pii are similar to the batches tested (b) (4) Therefore, the comparative in vitro release testing supports the addition of the (b) (4) testing site.

Primary Biopharmaceutics Reviewer Name and Dates:
Kelly M. Kitchens, Ph.D., October 23, 2018

Secondary Biopharmaceutics Reviewer Name and Dates:
Okpo Eradiri, Ph.D. 10/25/2018

Kelly Kitchens

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Okponanabofa Eradiri

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MICROBIOLOGY

Product Background:

ANDA: 210136

Drug Product Name / Strength: BRIXADI (buprenorphine extended-release), [8, 16, 24, 32mg-week; 64, 96, 128mg-month].

Route of Administration: Subcutaneous Injection.

Applicant Name: Braeburn Pharmaceuticals, Inc.

Manufacturing Site: Pharmaceutics International, Inc. (PII), 103 Beaver Court, Cockeysville, MD 21030.

Method of Sterilization: (b) (4).

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: The drug product is (b) (4)
(b) (4)

List Submissions Being Reviewed: 01/05/2018 and 05/23/2018.

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is **recommended** for approval on the basis of sterility assurance.

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

> Microbiology review N210136MR01.doc, dated 12/21/2017 for container closure system.

List Number of Comparability Protocols (ANDA only): None.

The NDA 210136 amendment dated 05/23/2018 responds to the Agency's deficiency letter (CR) dated 01/19/2018. The original comments are provided in italics below and are followed by the responses.

01/19/2018 Information Request: (b) (4)

(b) (4)

05/23/2018 Response: The applicant states that they were committed to provide results (b) (4)

(b) (4)

P.2 Pharmaceutical Development

(b) (4)

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Koushik Paul

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Elizabeth Bearr

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Date: 8/22/2018 02:50:13PM
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Valerie Amspacher

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Date: 12/07/2018 02:55:46PM
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Recommendation: Complete Response

NDA 210136

Review #1

Drug Name/Dosage Form	**CAM2038(buprenorphine)Injection**
Strength	**8, 16, 24, 32mg Weekly; 64, 96, 128.[(b) (4)]mg Monthly**
Route of Administration	**Subcutaneous**
Rx/OTC Dispensed	**Rx**
Applicant	**Braeburn Pharmaceuticals Inc.**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	7/19/2017	Drug Substance, Drug Product, Process, Facilities, Biopharmaceutics Microbiology
Amendment (SD 9)	8/23/2017	Drug Product, Process, Biopharmaceutics, Microbiology
Amendment (SD 22)	10/6/2017	Drug Substance, Drug Product, Microbiology
Amendment (SD 27)	10/13/2017	Biopharmaceutics
Amendment (SD 28)	10/13/2017	Drug Substance
Amendment (SD 32)	10/19/2017	Facilities
Amendment (SD 34)	10/25/2017	Drug Product
Amendment (SD 37)	10/30/2017	Facilities
Amendment (SD 38)	10/31/2017	Drug Product
Amendment (SD 39)	11/3/2017	Drug Product
Amendment (SD 41)	11/3/2017	Drug Product
Amendment (SD 43)	11/9/2017	Drug Product, Process, Biopharmaceutics, Microbiology
Amendment (SD 45)	11/14/2017	Drug Substance
Amendment (SD 47)	11/17/2017	Biopharmaceutics
Amendment (SD 51)	11/29/2017	Drug Product
Amendment (SD 56)	12/1/2017	Drug Product
Amendment (SD 58)	12/4/2017	Drug Product

Amendment (SD 59)	12/6/2017	Drug Product
Amendment (SD 60)	12/6/2017	Drug Product
Amendment (SD 61)	12/8/2017	Process, Microbiology
Amendment (SD)	12/14/2017	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	**Erika Englund**	**Donna Christner**
Drug Product	**Valerie Amspacher**	**Julia Pinto**
Process	**Pei-I Chu**	**Ubrani Venkataram**
Microbiology	**Daniel Schu/Elizabeth Bearr**	**John Arigo**
Facility	**Aditi Thakur/Derek Smith**	**Mahesh Ramanadham**
Biopharmaceutics	**An-Chi (Angela) Lu/Kelly Kitchens**	**Tapash Ghosh**
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	**Ciby Abraham**	
Laboratory (OTR)	N/A	
ORA Lead	**Cayrn McNab**	
CDRH-OC	**Philip Lafleur, Elijah Weisberg**	**Nazia Rahman**

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 II		(b) (4)	Active	11/9/17	
	Type II			Active	12/21/17	
	Type III			Active	12/21/17	
	Type III			Active	12/21/17	
	Type III			Active	12/21/17	
	Type IV			Active	12/21/17	Deficient -see DMF review
	Type IV			Active	12/21/17	
	Type V			Active	12/21/17	

B. Other Documents: *IND, RLD, or sister applications* **-N/A**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH	Complete	Inadequate	12/22/ 2017	Elijah Weisberg, Philip Lafleur, Nazia Rahman,

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on the recommendations from facilities, CDRH-OC, microbiology, biopharmaceutics, and drug product, CMC recommends a complete response for (b) (4) (CAM2038 q1w 8 mg/0.16 mL, CAM2038 q1w 16 mg/0.32 mL, CAM2038 q1w 24 mg/ 0.48 mL, CAM2038 q1w 32 mg/0.64 mL, CAM2038 q4w 64 mg/0.18mL, CAM2038 q4w 96 mg/0.27 mL, CAM2038 q4w 128 mg/ 0.36 mL, (b) (4) (b) (4) Drug substance and process recommends approval.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	CAM2038 drug products have been developed as (b) (4) extended release buprenorphine products indicated for the treatment of opioid use disorder with CAM2038 q1w targeted for once weekly administration and CAM2038 q4w targeted for once monthly administration. The product can be injected in the buttocks, abdomen, posterior upper arm or thigh.
Duration of Treatment	Once weekly to once monthly
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

CAM2038 (buprenorphine) Injection, q1w and q4w, subcutaneous depot drug product is a liquid formulation that contains buprenorphine base (b) (4) The CMC information for the drug substance buprenorphine base which is manufactured by (b) (4) is referenced in DMF# (b) (4). A letter of authorization was provided for the DMF and it was last reviewed and found adequate on 11/6/2017 by the drug substance reviewer Dr. Erika Englund for this NDA. Buprenorphine base is a white or almost white crystalline powder with a melting point range between 216-218°C. It is freely soluble in water (b) (4) (b) (4) The drug substance has a retest period of (b) (4) months (b) (4)

CAM2038 is available as a once weekly and once monthly extended-release solution for injection in a pre-filled syringe available in CAM2038 q1w 8 mg/0.16 mL, CAM2038 q1w 16 mg/0.32 mL, CAM2038 q1w 24 mg/ 0.48 mL, CAM2038 q1w 32 mg/0.64 mL, CAM2038 q4w 64 mg/0.18mL, CAM2038 q4w 96 mg/0.27 mL, CAM2038 q4w 128 mg/ 0.36 mL (b) (4) strengths. The CAM2038 FluidCrystal subcutaneous injection depot drug product is a yellowish to yellow clear liquid (b) (4) 1 mL long (b) (4) clear glass syringes with grey plungers. The drug product (b) (4)

(b) (4) During the microbiology review, Dr. Elizabeth Bearr noted that the applicant's container closure integrity test was not performed adequately. Without additional information on the testing procedure or an alternative test method, the microbiology group cannot assess the assurance of sterility of the product throughout its shelf life.

The CAM2038 q1w solution consists of 50 mg buprenorphine base (BUP)/mL, 10% w/w ethanol (EtOH) and Soybean Phosphatidylcholine (SPC)/Glycerol Dioleate (GDO) in the weight ratio 50/50 to final volume. The CAM2038 q4w solution consists of 356 mg buprenorphine base (BUP)/mL, 30% w/w N-methyl-2-pyrrolidone (NMP), and SPC/GDO in the weight ratio 40/60 to the final volume. The injection products utilizing the lipid-based formulations are low viscosity liquids. When the product is injected into the subcutaneous tissue, the formulation absorbs interstitial aqueous body fluid and transforms the liquid to a highly viscous gel. According to the applicant. (b) (4)

CAM2038 q1w and CAM2038 q4w drug product. The applicant provides release and stability data for the low viscous liquid but only performs dissolution testing for the high viscous gel. Though the applicant clearly mentions that the (b) (4)

the applicant does not provide an assay or any controls for the (b) (4) release or stability. The applicant references DMF# (b) (4) (b) (4) but the DMF is currently deficient for this application. The biopharmaceutics team reviewed the dissolution method and found the method and results to be adequate to support the release of the 1 week and 4 week formulations. This assessment by the biopharmaceutics group of the dissolution method and results is critical for CMC. (b) (4) (b) (4) In a recent inspection on 11/6/2017 of Pharmaceutics International, Inc. (Pii), FEI# 1000513101, the Office of Regulatory Affairs (ORA) investigators inspected the testing laboratory of the drug product and issued a 483 and recommended a withhold to the site for this application. The withhold recommendation from ORA was confirmed by the Office of Process and Facilities. One of the most concerning observations that were found at the site directly related to the dissolution method and results. A summary of the facility findings for the dissolution method and results are summarized below by the facility reviewer, Dr. Derek Smith:

(b) (4)

(b) (4)

With these unresolved issues for the dissolution method and results, the biopharmaceutics and facilities group cannot recommend approval until Pii resolves their issues. Other issues were observed at the testing site which is documented in Dr. Derek Smith's facility review. The resolution of these issues and re-inspection of the site will be necessary to recommend approval. In addition, CDRH-OC recommends withhold of the firm for not complying with 21 CFR 820 to meet the requirements of 21 CFR Part 4. Their review was placed in DARRTS on 12/22/2017.

Other CMC deficiencies have been identified. The applicant did not provide an adequate extractables and leachables study report. The applicant has not provided freeze/thaw data for the drug product and no stability data on the upright and inverted storage conditions of the product. It is also not clear if the dose delivered testing is representative of the dose delivered to the patient. The ethanol content for the q1w formulation is wide and needs to be tightened.

CMC recommends a complete response until all deficiencies are resolved. Below is the list of CMC deficiencies.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

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 • Process parameters • Scale/equipment • Site	L	-	N/A	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	-	Medium	This application is recommended for a CR. See micro deficiency.
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	High	This application is recommended for a CR. See facility deficiencies.

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

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Ciby Abraham

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BIOPHARMACEUTICS

Product Background:
Pursuant to 505(b)(2) pathway, the Applicant submits an NDA for (b) (4) (buprenorphine), a subcutaneous injection intended for opioid use disorder (OUD) and (b) (4) should be used as part of a complete treatment plan to include counseling and psychosocial support. The clinical study program was designed to evaluate efficacy across treatment phases (initiation, stabilization, and maintenance) and including both treatment-seeking adults with OUD, and patients transferred from treatment with daily sublingual (SL) buprenorphine (BPN) and transmucosal BPN/naloxone (NX) products. This NDA received priority review based on the fact that the product virtually eliminates the potential for abuse because it is administered by clinicians only and never dispensed to patients. (b) (4) is available as a Once Weekly and Once Monthly extended-release solution for injection in a pre-filled syringe available in 8 mg, 16 mg, 24 mg, 32 mg, 64 mg, 96 mg, 128 mg. (b) (4)

NDA/ANDA: 210136

Drug Product Name / Strength: Buprenorphine subcutaneous injection, 50 mg/mL and 356 mg/mL

Route of Administration: Injection

Applicant Name: Braeburn Pharmaceuticals

Review Recommendation: From Biopharmaceutics perspective, NDA for (b) (4) (buprenorphine) subcutaneous injection is considered ***Inadequate*** due to the Office of Process and Facilities findings of the Pharmaceutics International Inc. (Pii), Hunt Valley, facility.

List Submissions being reviewed:

July 19, 2017	Sequence 0002 - 0002 (2) 07/19/2017 ORIG-1 /Multiple Categories/Subcategories
August 23, 2017	Sequence 0009 - 0009 (9) 08/23/2017 ORIG-1 /Quality/Response To Information Request
October 13, 2017	Sequence 0028 - 0028 (27) 10/13/2017 ORIG-1 /Quality/Response To Information Request
November 9, 2017	Sequence 0043 - 0043 (43) 11/09/2017 ORIG-1 /Quality/Response To Information Request
November 17, 2017	Sequence 0047 - 0047 (47) 11/17/2017 ORIG-1

	/Quality/Response To Information Request

Review Summary:

Formulation Development

Both the CAM2038 50 mg/mL buprenorphine q1w and 356 mg/mL buprenorphine q4w FluidCrystal® subcutaneous injection depot (hereinafter denoted CAM2038 q1w and CAM2038 q4w) drug products are a sterile (b) (4) yellowish to yellow clear liquid (b) (4) 1 mL long clear glass syringes with grey plungers. The drug product is a lipid-based parenteral (subcutaneous injection) extended release product (once weekly and once monthly dosing) based on the proprietary FluidCrystal® (hereinafter denoted FC) injection depot technology. The qualitative and quantitative composition of q1w and q4w FluidCrystal® subcutaneous injection depot is listed in Table 1 and Table 2, respectively.

Table 1: Composition of CAM2038 q1w Drug Product

Component	Standard	Function	Composition (mg) per dose			
			8 mg/ 0.16 mL	16 mg/ 0.32 mL	24 mg/ 0.48 mL	32 mg/ 0.64 mL
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	8	16	24	32
Ethanol Anhydrous (Dehydrated alcohol) (EtOH)	USP	(b) (4)				
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					

Table 2: Composition of CAM2038 q4w Drug Product

Component	Standard	Function	Composition (mg) per dose			(b) (4)
			64 mg/ 0.18 mL	96 mg/ 0.27 mL	128 mg/ 0.36 mL	
Buprenorphine Base (BUP)	Ph. Eur.	Active ingredient	64	96	128	
N-Methyl-2-Pyrrolidone (NMP)	USP	(b) (4)				
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					

Manufacturing site change

The same CAM2038 q1w and CAM2038 q4w formulations have been used for Phase 1 through Phase 3 of the clinical development program. The drug substance and drug product manufacturing sites were changed during development.

The comparative in vitro release test for bridging between the pre-change (b) (4)

(b) (4) and post-change (Pharmaceutics International Inc., 103 Beaver Court, Cockeysville, MD 21030, USA) manufacturing sites showed that the f2 values were ≥ 50 for all respective profiles for both CAM2038 q1w and CAM2038 q4w, and fulfills the requirement of f2 > 50 (50-100), thus indicating a level of "sameness" of the in vitro release profiles for the product manufactured at the respective sites. Therefore the manufacturing site change is acceptable.

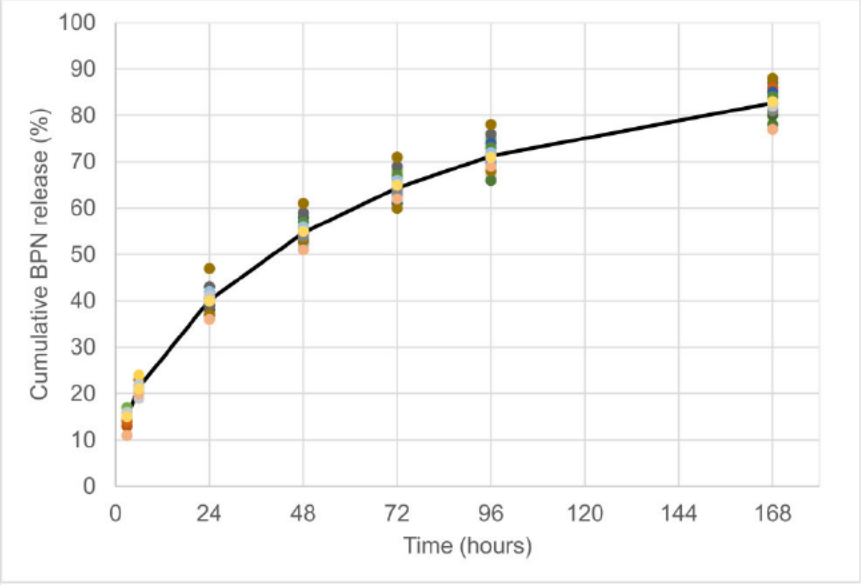
In Vitro Release Testing
Apparatus: Apparatus 1 (basket)
Speed: 50 rpm at temperature 37°C ± 0.5°C
Medium for CAM2038 q1w: Citric acid buffer, 100 mM, pH 3.0, 900 mL
Medium for CAM2038 q4w: Citric acid buffer, 100 mM, pH 4.0, 500 mL

Acceptance Criteria for CAM2038 q1w:
Level 1:
(b) (4)
(b) (4) % released at 6 hours
(b) (4) % released at 48 hours
NLT (b) (4) % released at 168 hours

Level 2:
(b) (4)

Figure 1 below shows the in vitro release data for CAM2038 q1w (mean values) obtained for clinical Phase 3 and formal stability batches at release and upon stability. The in vitro release data meet the proposed acceptance criteria.

Figure 1: In vitro release data for CAM2038 q1w (mean values) obtained for clinical Phase 3 and formal stability batches at release and upon stability. The fully drawn line represents the overall mean ("Mean of means", n = 82).



Interim Acceptance Criteria for CAM2038 q4w:

Level 1:

(b) (4)

NMT (b) (4) % released at 1 hour

(b) (4) % released at 6 hours

(b) (4) % released at 24 hours

NLT (b) (4) % released at 48 hours

Level 2:

(b) (4)

The applicant commits to submit a Prior Approval Supplement to replace the interim 24-hr and 48-hr IVR specification limits for Q4W proposed in this response with limits set at 12 hours and 72 hours using data generated from the pivotal clinical and registration stability batches, including the remaining stability time points, and the process performance qualification (PPQ) batches. In the action letter, the applicant will be advised to submit this data in either the Annual Report or a Post-Approval Supplement, whichever one occurs first, and the final acceptance criteria will be decided upon review of that data by the Agency.

Preliminary In Vitro-In Vivo Correlation (IVIVC)

A preliminary in vivo and in vitro correlation was assessed using cumulative area under the curve (AUC) of the plasma concentration data in the human PK studies and in vitro release data for both CAM2038 q1w and q4w. However, the IVIVC is preliminary and not finalized. This preliminary IVIVC model shall not be used to

support future submissions (such as biowaiver) unless a final IVIVC model is finalized, submitted for review, and approved by the Agency.

Extended Release Claim
The Applicant submitted adequate information to support the extended-release claim per 21 CFR 320.25f:

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

In Vitro Release Method and Acceptance Criteria

Reviewer's Assessment: ***Inadequate***

Formulation Design:
The CAM2038 (buprenorphine) Injection, q1w and q4w, subcutaneous depot drug product (hereinafter denoted CAM2038 q1w and CAM2038 q4w) is a liquid formulation with the buprenorphine base drug substance (b) (4) (b) (4) The liquid formulations are a lipid-based parenteral (subcutaneous injection) extended release product based on the proprietary FluidCrystal® (hereinafter denoted FC) injection depot technology. Injection products utilizing the lipid-based FC technology are relatively low viscosity liquids, typically in the (b) (4) mPas range, in which the drug substance is dissolved. When injected into the subcutaneous (SC) or intramuscular (IM) tissue, the FC formulation absorbs interstitial aqueous body fluid and transforms from liquid to highly viscous ((b) (4) mPas) liquid crystal (LC) (or gel-like) phases in situ.

(b) (4)

The identification of the most suitable lipid composition range for long-acting release products based on FC depot release properties was performed through the use of in vitro release experiments utilizing both model drug substances (b) (4) and active pharmaceutical ingredients.

Development of CAM2038 q1w Formulation

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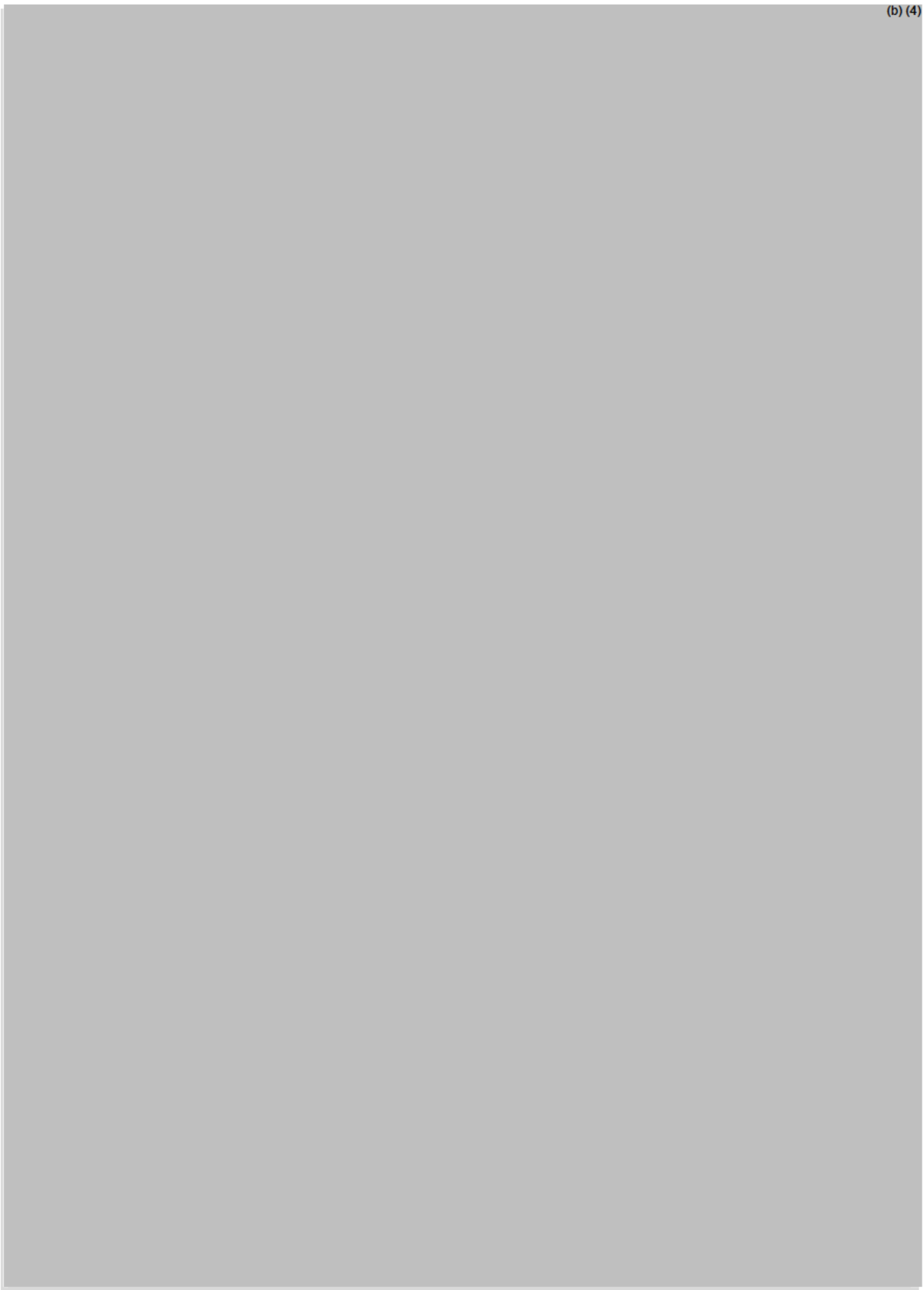
(b) (4)

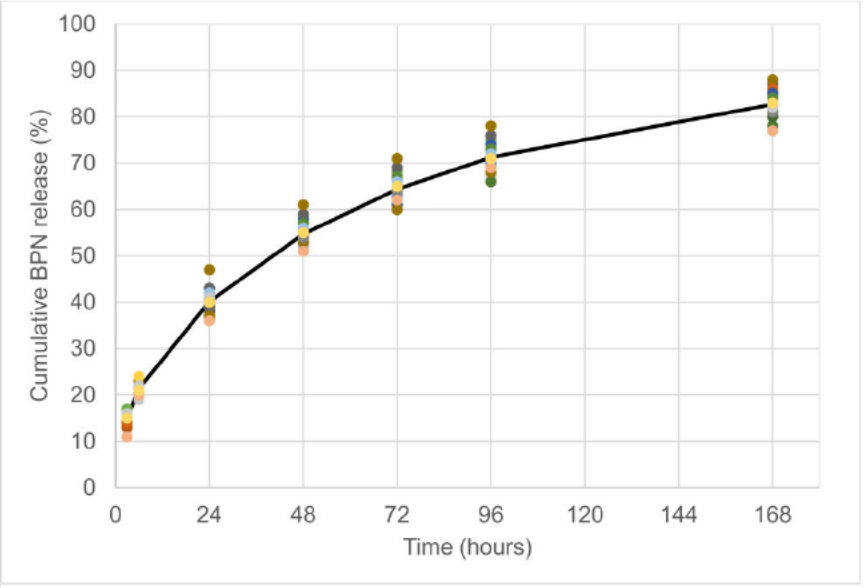


In vitro release Data and Profiles

CAM2038 q1w:

The different strengths of the CAM2038 q1w drug product, i.e., 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL and 32 mg/0.64 mL, are accomplished by different fill volumes in the final pre-filled syringe primary packaging. Hence, the drug product formulation composition is identical for all strengths. In addition, the injection volume of 0.16 mL (= 8 mg buprenorphine) is used in the in vitro release testing for all strengths/fill volume. Therefore, the in vitro release data from clinical phase 3 and formal stability batches of the different strengths are pooled and represented below in Figure 6. The in vitro release profile of different strengths and different time points during stability studies appear to be similar and therefore pooling of the in vitro release data seems reasonable. The mean in vitro release profile appears to be consistent through all clinical Phase 3 and formal stability batches.

Figure 6: In vitro release data for CAM2038 q1w (mean values) obtained for clinical Phase 3 and formal stability batches at release and upon stability. The fully drawn line represents the overall mean ("Mean of means", n = 82).



Acceptance Criteria for CAM2038 q1w:

Level 1:

(b) (4)

(b) (4)% released at 6 hours

(b) (4)% released at 48 hours

NLT (b) (4)% released at 168 hours

Level 2:

(b) (4)

The proposed specification ranges for initial and middle time points represent a mean target value ± (b) (4)% of label claim. At the final time point of 168 hours, the data showed

that the mean value is 83% buprenorphine release (SD = 2%) with a range of observed mean values of 77-89%. The acceptance criterion of not less than (b) (4)% at 168 hours (b) (4) represents approximately the observed overall Mean (83%) - 3·SD. The human in vivo data show that about 81% (mean value; SD = 7%; n = 18) with a range of 56-92% of the overall exposure (cumulative AUC (AUC_{cum})) is realized at 168 hours for the 8 mg (0.16 mL) dose.

The applicant noted that (b) (4) the acceptance criteria was due to the (b) (4)

An Information Request (IR) was sent to the applicant on 10/26/2017 as follows:
According to the FDA guidance, for extended release oral dosage forms, the last time point should be the time point where at least 80% of drug has dissolved. Therefore, for the in vitro release acceptance criteria for CAM2038 q1w, we recommend that the drug release at the last time point (168 hours) is NLT 80%.
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ UCM070239.pdf).

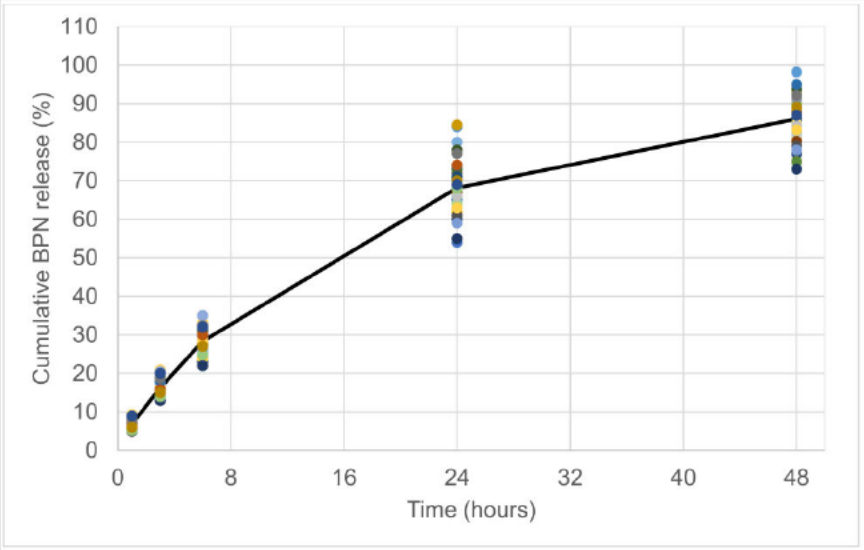
The applicant responded on 11/9/2017 by showing the in vitro release data from clinical Phase 3 and formal stability batches for CAM2038 q1w formulation. (b) (4)

Reviewer's comments:
The applicant only tested two batches at the L2 level (i.e. n=12). All the other batches tested at release and stability pass the applicant's proposed specification of NLT (b) (4)% released in 168 hours at the L1 level, but it cannot be determined if these batches would pass the FDA-recommended specification of NLT 80% released in 168 hours at the L2 level since only n=6 units were tested for the clinical and stability batches. Considering the lipid-based, poorly soluble drug product formulation, and the in vitro release data submitted, the applicant's proposed specification of NLT (b) (4)% released at 168 hours is adequate.

<u>CAM2038 q4w:</u>
The different strengths of the CAM2038 q4w drug product, i.e., 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL (b) (4) are accomplished by different fill

volumes in the final pre-filled syringe primary packaging. Hence, the drug product formulation composition is identical for all strengths. In addition, the injection volume of 0.18 mL (= 64 mg buprenorphine) is used in the in vitro release testing for all strengths/fill volume. Therefore, the in vitro release data from clinical phase 3 and formal stability batches of the different strengths are pooled and represented below in Figure 6. The in vitro release profile of different strengths and different time points during stability studies appear to be similar and therefore pooling of the in vitro release data seems reasonable. The mean in vitro release profile appears to be consistent through all clinical Phase 3 and formal stability batches.

Figure 7: In vitro release data for CAM2038 q4w (mean values) obtained for clinical Phase 3 and formal stability batches at release and upon stability. The fully drawn line represents the overall mean ("Mean of means", n = 47).



Acceptance Criteria for CAM2038 q4w (originally proposed by the applicant):

Level 1:

(b) (4):

NMT (b) (4)% released at 1 hour

(b) (4)% released at 6 hours

NLT (b) (4)% released at 72 hours

Level 2:

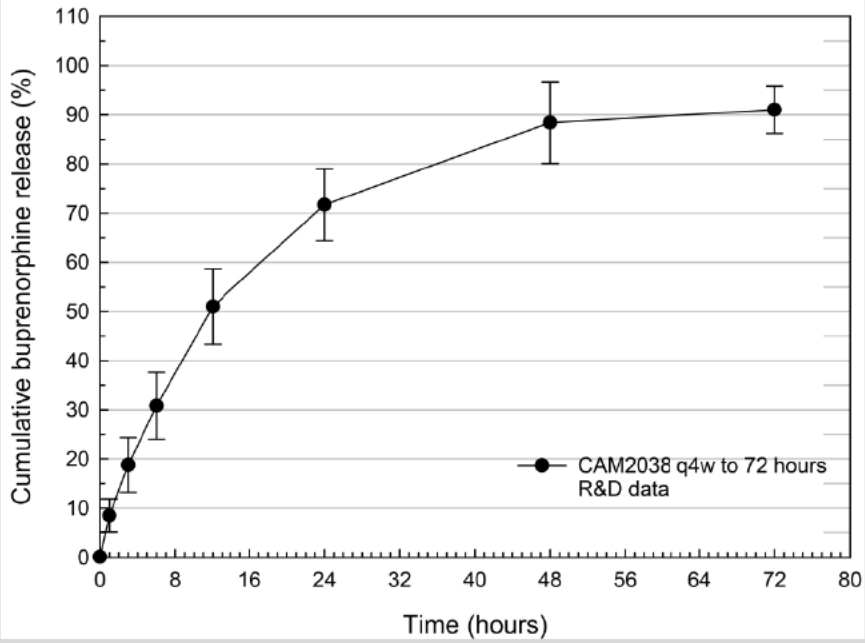
(b) (4)

The proposed specification limit covers initial and terminal phases of the in vitro release profile with not less than (b) (4)% of drug dissolved for the last specification time point. The acceptance criterion for the initial time point at 1 hour is set to not more than (b) (4)%. (b) (4)

This initial time point acceptance criterion corresponds to the observed overall mean of

(b) (4)% and the range of mean values determined for the clinical Phase 3 and formal stability batches is (b) (4)%. The acceptance criterion for the middle time point at 6 hours represents a mean target value of (b) (4)% of label claim. The last time point was set according to the FDA recommendation of setting the specification for the last time point was required at not less than (b) (4)% released buprenorphine. The applicant therefore extended the last time point from 48 hours to 72 hours. An in vitro release profile up to 72 hours for CAM2038 q4w is shown in Figure 8 which met the specification limit of not less than (b) (4)% at 72 hours.

Figure 8: In vitro release data for CAM2038 q4w formulation (mean values ± SD, n = 6) up to 72 hours.



In an Information Request (IR) letter sent to the applicant dated 8/8/2017, the FDA requested the following question:

For the CAM2038 q4w formulation, the in vitro release method only evaluates in vitro drug release for 48 hours while the product is formulated for once a month injection. In the written responses only meeting minutes dated 12/6/2016, we recommended that you develop a long-term in vitro release (IVR) method for CAM2038 q4w. It should be discriminative and should account for at least (b) (4)% release of the labelled amount of drug. Please develop a long term in vitro release method and submit the method development report and data for CAM2038 q4.

The applicant responded on 8/23/2017 that the final in vitro release test method was proposed to be conducted to 72 hours with a specification of NLT (b) (4)% released at the final (72 hour) test time point in accordance with the advice from the FDA.

Reviewer's comments:
The last time point at 72 hours for the in vitro release specification satisfies the FDA's

request for CAM2038 q4w for at least (b)(4)% release of the labelled amount of drug. Therefore the applicant's response is adequate. However, an IR dated 10/26/2017was sent to the applicant as follows regarding the acceptance criteria:

"For the in vitro release acceptance criteria for CAM2038 q4w, in order to ensure quality control of your product from (b)(4)% to complete release, we believe an additional in vitro release time point at 24 hours is necessary for CAM2038 q4w. We recommend that you propose a specification at the 24-hour time point per the in vitro release data at release and stability.

You do not have sufficient data to support the proposed in vitro release acceptance criterion at 72 hours for CAM2038 q4w. Since there are in vitro release data for pivotal clinical batches and registration stability batches at release and stability at 48 hours, the following interim in vitro release acceptance criteria are recommended based on the in vitro release data submitted for CAM2038 q4w:

1 hour: NMT (b)(4)% released
6 hours: (b)(4)% released
24 hours: to be proposed by Applicant
48 hours: NLT (b)(4)% released

If you want to include an in vitro release acceptance criterion time point at 72 hours, you need to submit the complete in vitro release data from pivotal clinical batches and registration stability batches at release and stability."

In the November 17, 2017 IR response, the applicant presented the release and stability data for in-vitro release testing (IVR) for CAM2038 q4w pivotal clinical and registration stability batches. This data set covers five (5) unique pilot-scale compounding batches used to fill ten (10) drug product (fill) batches of various fill volumes (strengths). These five compounding batches used two lots (b)(4) (b)(4) as shown below:

Table 6: Summary of (b)(4) Lots for CAM2038 Q4W

Compounding Batch	Pii Lot #	(b)(4) Lot #	Pii Lot #	(b)(4) Lot #	Filling Lot
23517.001	14-0859	1140696-14	14-0169	PP2/898	23518.001
					23519.001
23517.002	14-0269	1130690-01	14-0820	PP1/911	23519.002
					23521.002
23520.001	14-0859	1140696-14	14-0169	PP2/898	23521.001
					23522.001
23520.002	14-0269	1130690-01	14-0820	PP1/911	23518.002
					23522.002
23520.003	14-0269	1130690-01	14-0820	PP1/911	23518.003*
					23522.003*

* Non-clinical batches used for stability studies only.

24-hr Test Point

The overall mean of the IVR data for the 24-hr test point is 68% with a standard deviation of 6.7%. The applicant used a statistical normal tolerance interval analysis for the 24-hr test point with 99% coverage and 95% confidence interval, and the result

is a range of (b) (4) *%.*

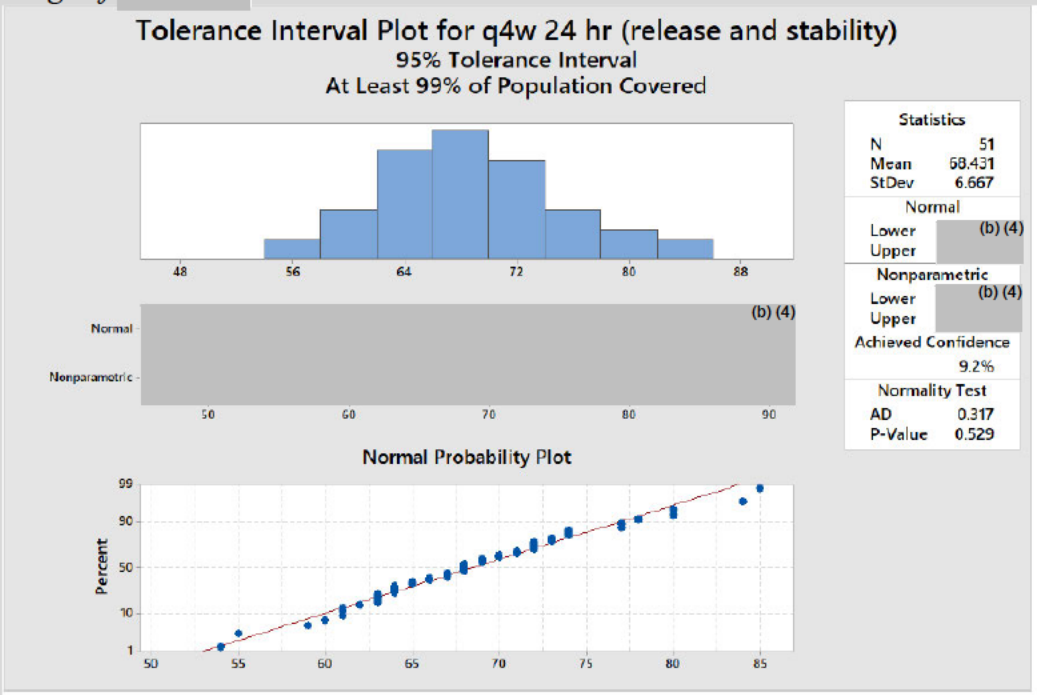


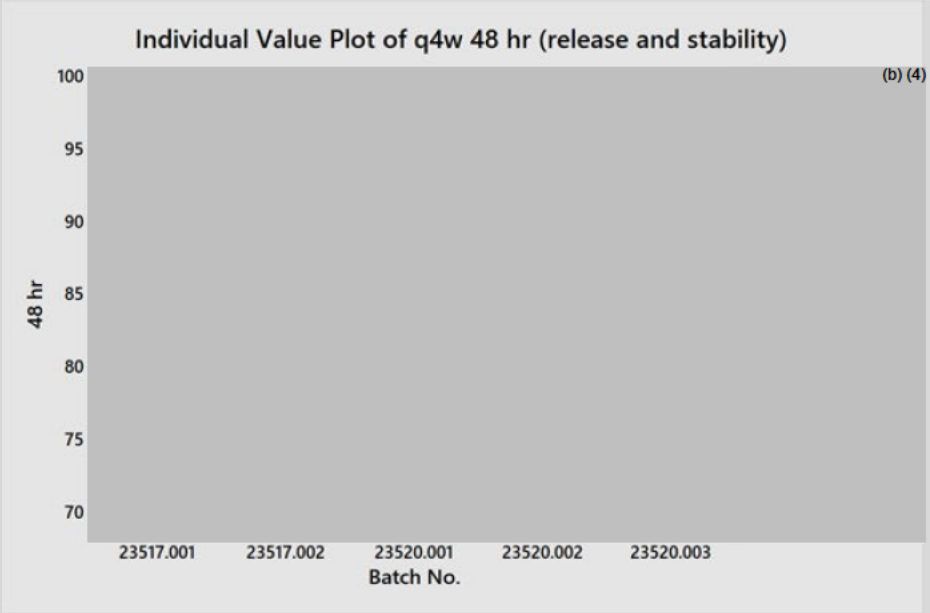
Figure 1: **Normal Tolerance Interval (95%/99%) Q4W – 24-hr Test Point - All Release and Stability Data**

48-hr Test Point

The overall mean at the 48-hr test point is 86% with a standard deviation is 5.8%. The applicant used a statistical normal tolerance interval analysis for the 48-hr test point with 99% coverage and 95% confidence interval, and the result is a lower limit of NLT (b) (4) *%. The applicant plotted the release and stability data by compounding batch with FDA's proposed specification of NLT* (b) (4) *% and applicant's proposed NLT* (b) (4) *% as illustrated below in* ***Figure 10****. All data would meet the NLT* (b) (4) *% acceptance criterion, but not the NLT* (b) (4) *% acceptance criterion.*

The applicant explained (b) (4)

Figure 10: Individual Dissolution Data for Q4W – 48-hr Test Point - All Release and Stability Data by Compounding Batch with Braeburn Proposed Interim Specification Limit and FDA Proposed Specification



In summary, the proposed interim IVR specification limit for CAM2038 Q4w is as follows:

1 hour: NMT (b) (4) *% released*
6 hours: (b) (4) *% released*
24 hours: (b) (4) *% released*
48 hours: NLT (b) (4) *% released*

The applicant commits to collect these data to support the 72-hour test point by testing the pivotal clinical and registration stability batches at remaining stability time points, and the recently manufactured process performance qualification (PPQ) batches. The applicant also proposes to collect data at a 12-hr test point on the same batches described above to replace the 24-hr test point, i.e., around a mean of 50% released buprenorphine, of the extended release profile compared to the 24-hour time point. The applicant proposes to submit a Prior Approval Supplement to replace the interim 24-hr and 48-hr IVR specification limits for Q4W proposed in this response with limits set at 12 hours and 72 hours using data generated from the pivotal clinical and registration stability batches, including the remaining stability time points, and the PPQ batches. A summary of the proposal is provided in Table 7.

Table 7: Summary of Proposed Interim and Post-Approval IVR Specification Limits for CAM2038 Q4W

Test Point	Interim Specification FDA Proposed (% Released)	Interim Specification Braeburn Proposed (% Released)	Test Point	Post Approval (PAS) Braeburn Proposed (% Released)
1 hr	NMT (b) (4)%	NMT (b) (4)%	1 hr	NMT (b) (4)%
6 hr	(b) (4)%	(b) (4)%	6 hr	(b) (4)%
24 hr	To Be Proposed	%	12 hr	TBD*
48 hr	NLT (b) (4)%	NLT (b) (4)%	72 hr	TBD*

* TBD = To be determined based on data from pivotal clinical and registration stability batches at remaining time points and PPQ batches

Reviewer's comments:
The applicant's interim IVR acceptance criteria for CAM2038 Q4w are too liberal. However, the applicant's proposal to submit data generated from the pivotal clinical and registration stability batches, including the remaining stability time points, and the PPQ batches, to replace the interim 24-hr and 48-hr IVR using is acceptable. In the action letter, the applicant will be advised to submit this data in either the Annual Report or a Post-Approval Supplement, whichever one occurs first. A final determination on the acceptability of the IVR acceptance criteria will be made based on the totality of the IVR data.

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

Reviewer's Assessment: *N/A*

Preliminary In Vitro-In Vivo Correlation (IVIVC)

CAM2038 q1w:

A preliminary in vivo and in vitro correlation was assessed using cumulative AUC of the plasma concentration data in the human PK studies and in vitro release data. The mean in vitro release profile from averaging profiles for Phase 3 batches and stability batches (n=82) is compared to the in vivo results on cumulative AUC (AUC_{cum}) obtained in the Phase 1 PK study (clinical study no. HS-11-426, n =18), and is illustrated in Figure 9. It is noted that the cumulative AUC for the 8 mg dose in vivo reached about 81% at day 7, which is similar to the overall mean in vitro release level at the same time point (83%) obtained for clinical Phase 3 and registration stability batches. When plotting the cumulative AUC (AUC_{cum}) against the cumulative in vitro drug release (%) from injection of 0.16 mL (8 mg) of the q1w formulation (Figure 10), it appears to have a linear relationship with r^2 of 0.983.

No formal in vitro in vivo correlation (IVIVC) model for CAM2038 q1w has been developed.

Figure 9: Cumulative AUC (AUC_{cum}) and cumulative in vitro drug release (%) from injection of 0.16 mL (8 mg) of the CAM2038 q1w formulation.

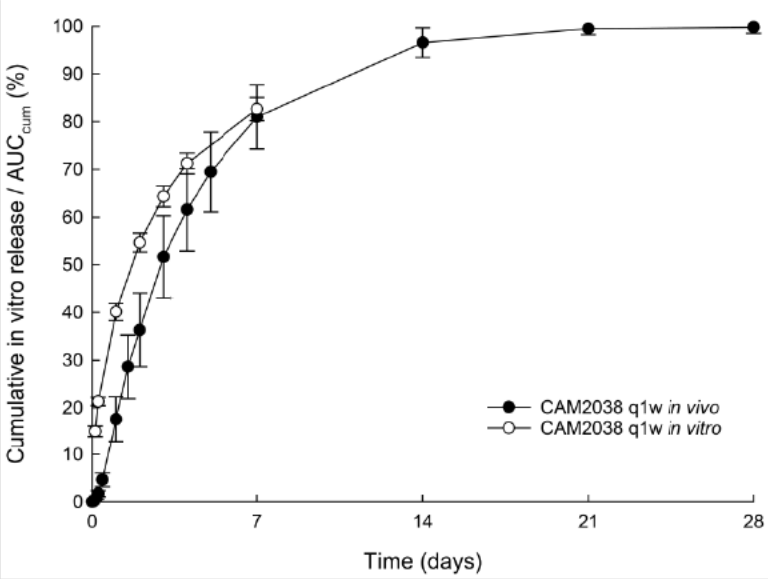
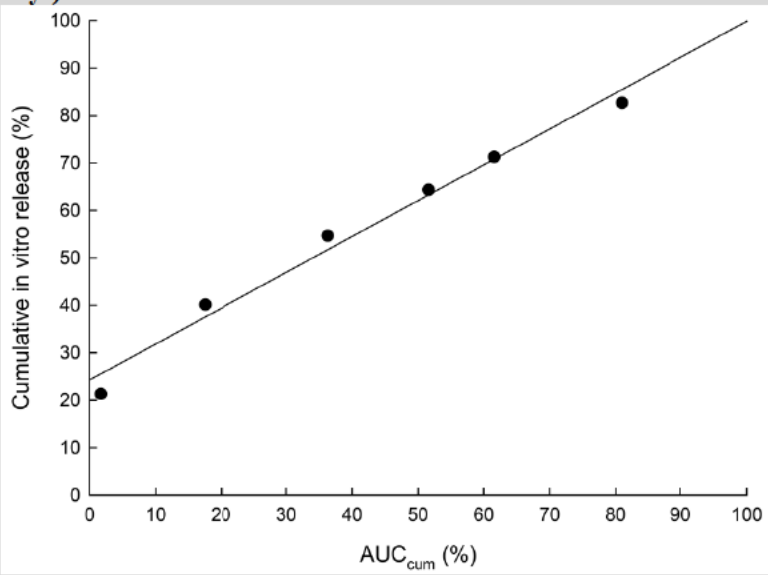


Figure 10: Cumulative in vitro drug release versus cumulative AUC (AUC_{cum}) (%) from injection of 0.16 mL (8 mg) CAM2038 q1w formulation at the indicated time points (0.25, 1, 2, 3, 4, and 7 days).



CAM2038 q4w:

A preliminary in vivo and in vitro correlation was assessed using cumulative AUC of the plasma concentration data in the human Phase 1 PK study (clinical study no. HS-13-487) and in vitro release data. Because of the different time scales, the in vitro release data were time transformed such that the release at the last time point (48 hours with an overall mean of 86% cumulative release) corresponds to the same level of the cumulative (%) AUC. This was found to be at day 49 in vivo where approximately 86% cumulative AUC was obtained. Hence, a factor of 49 days/48 hours = 1.02 days/hour was used to time transform the in vitro data. The preliminary result is shown in Figure 11. When plotting the cumulative AUC (AUC_{cum}) against the cumulative in

vitro drug release (%) from injection of 0.18 mL (64 mg) of the q4w formulation (Figure 12), it appears to have a linear relationship with r^2 of 0.996. No formal in vitro in vivo correlation (IVIVC) model for CAM2038 q4w has been developed.

Figure 11: Cumulative AUC and cumulative in vitro drug release (%) resulting from injection of 0.18 mL (64 mg) of CAM2038 q4w. Note that the time scale for the in vitro release data was transformed with a factor 1.02 days/hour as described in the text. Means ± SD (n = 17 in vivo and n = 47 in vitro).

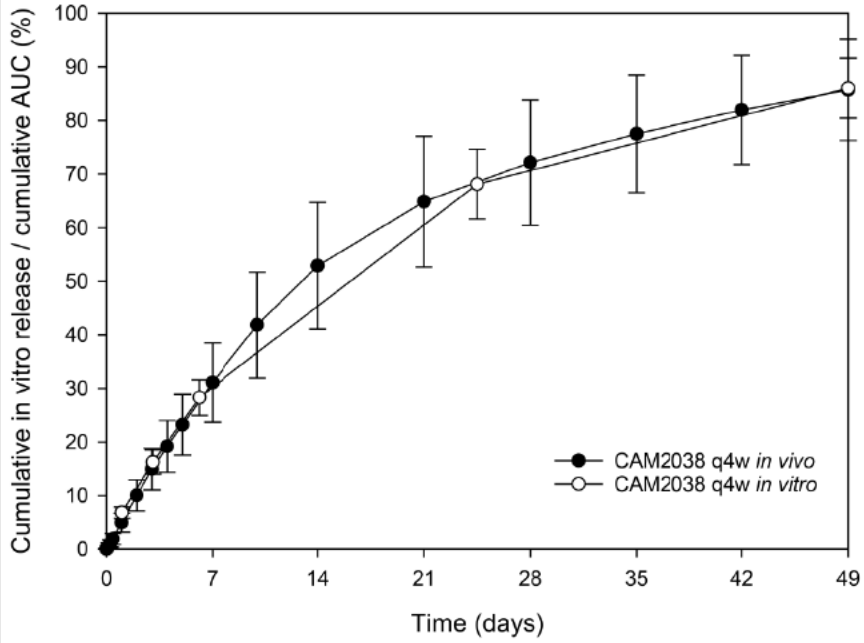
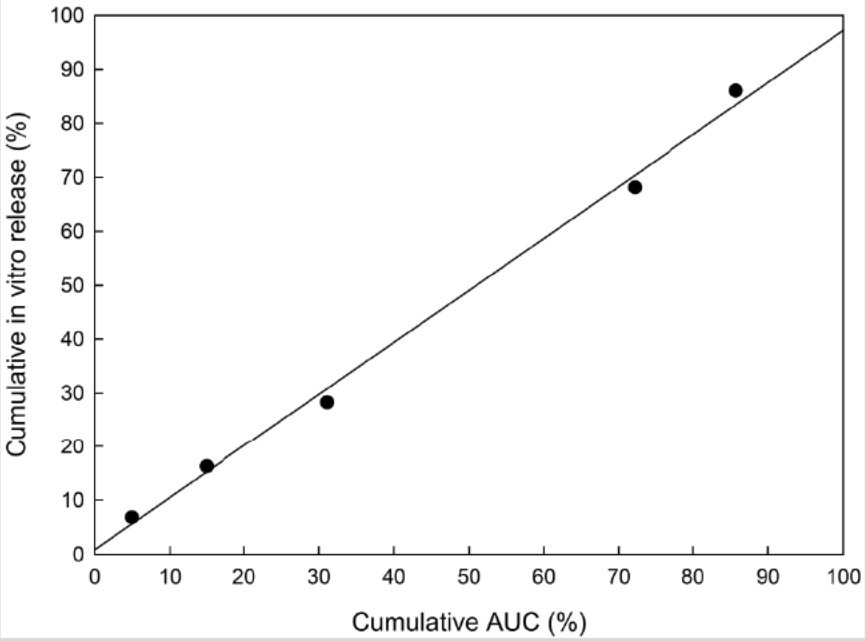


Figure 12: Overall mean in vitro drug release versus mean cumulative (%) AUC (AUCcum) resulting from injection of 0.18 mL (64 mg) CAM2038 q4w at specific times (1, 3, 7, 28, 49 days). Note that the time scale for the in vitro release data was transformed with a factor 1.02 days/hour as described in the text. Linear regression analysis resulted in a coefficient of determination, r2, of 0.996.



Reviewer's comments:
The IVIVC model is preliminary and not finalized. This preliminary IVIVC model shall not be used to support future submissions (such as biowaiver) unless a final IVIVC model is finalized, submitted for review and approved by the Agency.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: ***Adequate***

An Information request (IR) was sent to the applicant on 10/2/2017 as follows:

The following information should be submitted collectively to support the extended release designation claim (also refer to 21 CFR 320.25f):

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

The applicant responded on 10/13/2017 as follows:

The Buprenorphine bioavailability profiles (expressed as cumulative percent area under the plasma concentration-time curve (%AUC) is shown below in Figure 13 and Figure

14, respectively. The bioavailability profiles show that only a small fraction of the total buprenorphine exposure is released during the first 24 hours after dosing, and there is no dose dumping.

Reviewer's comments:
A follow-up IR was sent to the applicant on 11/9/2017 as follows:
"In your response to the IR letter dated 10/13/2017, you stated that the bioavailability profiles of Buprenorphine show that only a small fraction of the total buprenorphine exposure is released during the first 24 hours after dosing, and there is no dose dumping. The Buprenorphine bioavailability profiles were expressed as cumulative percent area under the plasma concentration-time curve (%AUC). Please clarify how bioavailability is expressed as cumulative percent area under the plasma concentration-time curve (%AUC)."

The applicant responded by reiterating that only a small fraction of the total buprenorphine exposure is released during the first 24 hours after dosing, and there is no dose dumping. In addition, it was noted that the absolute bioavailability of buprenorphine after administration of CAM2038 q1w and CAM2038 q4w was evaluated in the clinical studies HS-11-426 and HS-13-487. The pharmacokinetics of buprenorphine was evaluated after a single intravenous dose of buprenorphine and a SC dose of CAM2038 q1w or CAM2038 q4w administered to healthy volunteers. The absolute bioavailability of buprenorphine was estimated using dose-normalized area under the plasma concentration-time curve extrapolated to infinity (AUCinf/dose) values for intravenous buprenorphine and CAM2038 and not by using %AUC values. Complete absolute bioavailability of buprenorphine was observed for both CAM2038 products

Reviewer's comments:
This fulfills the first criterion of "The bioavailability profile established for the drug product rules out the occurrence of any dose dumping".

Figure 13: AUC_{cum} (%) vs. time following single SC administration of 8, 16, and 32 mg CAM2038 q1w (mean ± SD)

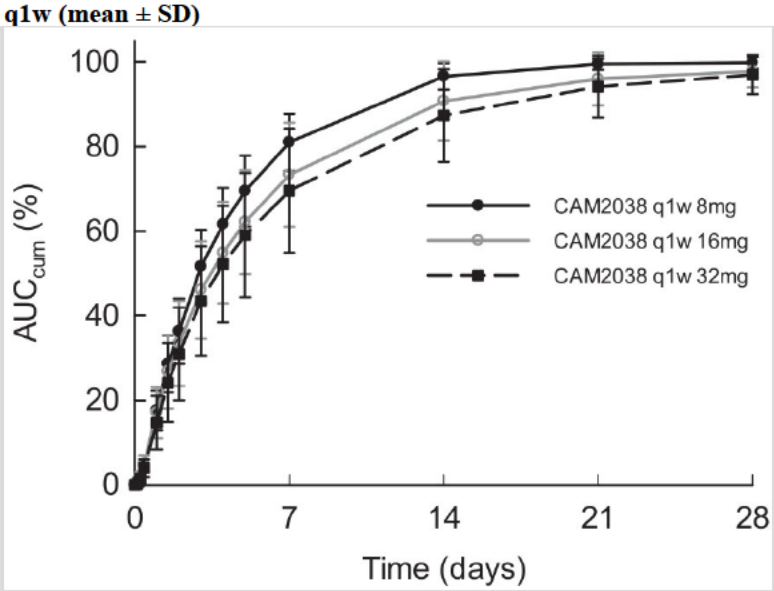
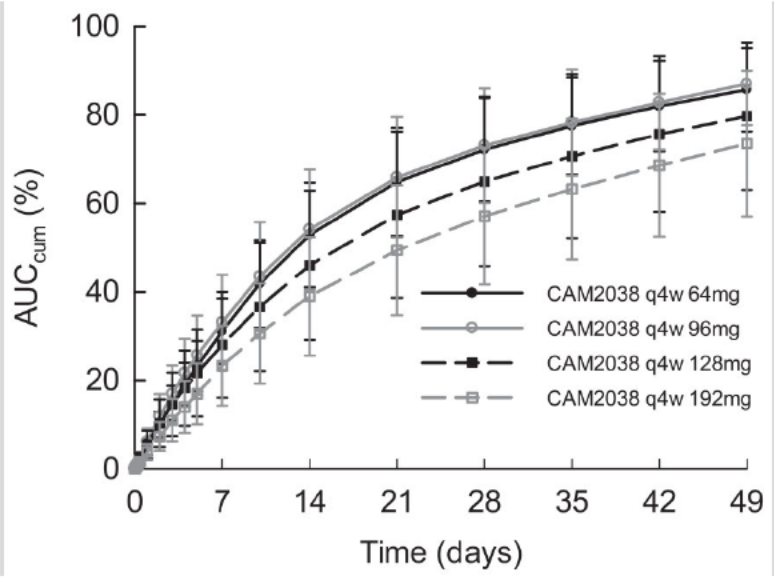


Figure 14: AUC_{cum} (%) vs. time following single SC administration of 64, 96, 128 mg, and 192 mg CAM2038 q4w (mean ± SD)



The Buprenorphine steady-state exposures for CAM2038 q1w and CAM2038 q4w were compared with Subutex (Buprenorphine sublingual (SL) tablet) with the degree of fluctuation shown below in Table 8. The degree of fluctuation for CAM2038 products range from 67.2% to 237%, whereas it ranges from 272% to 373% for Subutex products. The degree of fluctuation is lower for CAM2038 products compared to Subutex.

Reviewer's comments:

This fulfills the criterion of "The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA".

Table 8: Steady-state PK parameters of Buprenorphine after administration of repeated weekly CAM2038 q1w, repeated monthly CAM2038 q4w and repeated daily Subutex

Product Dose	Study No.	Population	Dose No.	Injection site	Parameter [geometric mean (geometric CV%)]			
					$C_{ss,max}$ (ng/mL)	$C_{ss,trough}$[a] (ng/mL)	$C_{ss,av}$ (ng/mL)	%Fluctuation
CAM2038 q1w 16 mg	HS-13-487	HV	4 (n=15)	Buttock	4.30 (44)	0.842 (22)	2.09 (24)	160 (36)
CAM2038 q1w 32 mg	HS-15-549	Patients	4-7 (n=21)	Buttock	6.87 (37)	2.63 (39)	4.17 (27)	95.3 (39)
	HS-15-549	Patients	4-7 (n=21)	Abdomen	6.56 (30)	2.68 (36)	3.91 (27)	98.3 (32)
	HS-15-549	Patients	4-7 (n=21)	Thigh	5.37 (44)	2.70 (48)	3.65 (37)	67.2 (45)
	HS-15-549	Patients	4-7 (n=21)	Upper arm	5.69 (43)	2.37 (37)	3.52 (34)	85.1 (48)
CAM2038 q4w 128 mg	HS-15-549	Patients	4 (n=16)	Buttock	11.1 (54)	2.09 (55)	3.89 (42)	220 (44)
CAM2038 q4w 160 mg	HS-15-549	Patients	4 (n=12)	Buttock	15.4 (52)	2.66 (61)	5.27 (26)	237 (80)
Subutex 8 mg	HS-11-426	HV	7 (n=18)	NA	4.74 (29)	0.606 (46)	1.13 (34)	373 (16)
	HS-13-487	HV	7 (n=17	NA	4.74 (36)	0.677 (52)	1.24 (33)	338 (30)
Subutex 16 mg	HS-11-426	HV	7 (n=15)	NA	6.25 (49)	0.794 (58)	1.60 (37)	347 (33)
	HS-13-487	HV	7 (n=15)	NA	6.72 (47)	1.05 (46)	1.90 (33)	308 (35)
Subutex 24 mg	HS-11-426	HV	7 (n=16)	NA	7.78 (37)	1.24 (44)	2.34 (29)	282 (34)
	HS-13-487	HV	7 (n=16)	NA	8.45 (54)	1.61 (40)	2.66 (34)	272 (27)

[a] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex

The plasma concentration-time profiles of CAM2038 show that the PK profiles are dose proportional with different dose of 8 to 32 mg for CAM2038 q1w and of 64 to 192 mg for CAM2038 q4w. The PK profiles are consistent and are illustrated below in Figure 14 and Figure 15 for CAM2038 q1w and CAM2038 q4w, respectively.

Reviewer's comments: This fulfills the criterion of "The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units".

Figure 15: Plasma concentration-time profiles of Buprenorphine after single SC injection of CAM2038 q1w (mean ± SD)

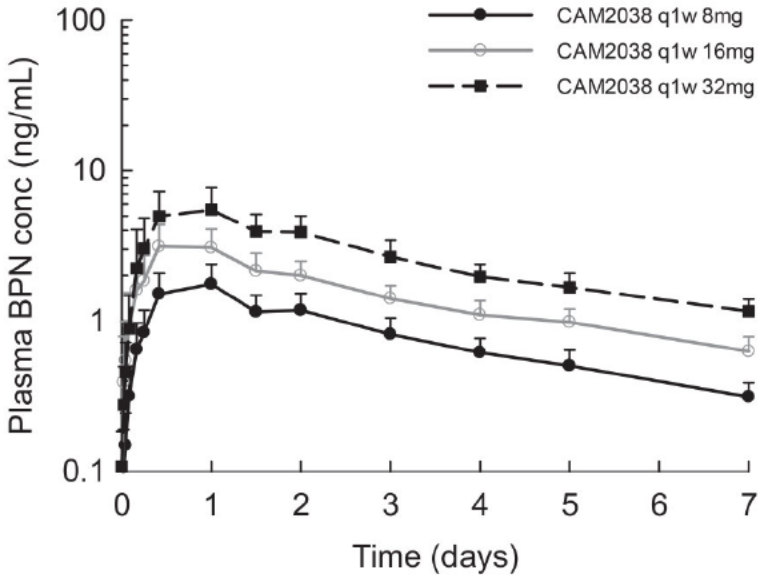
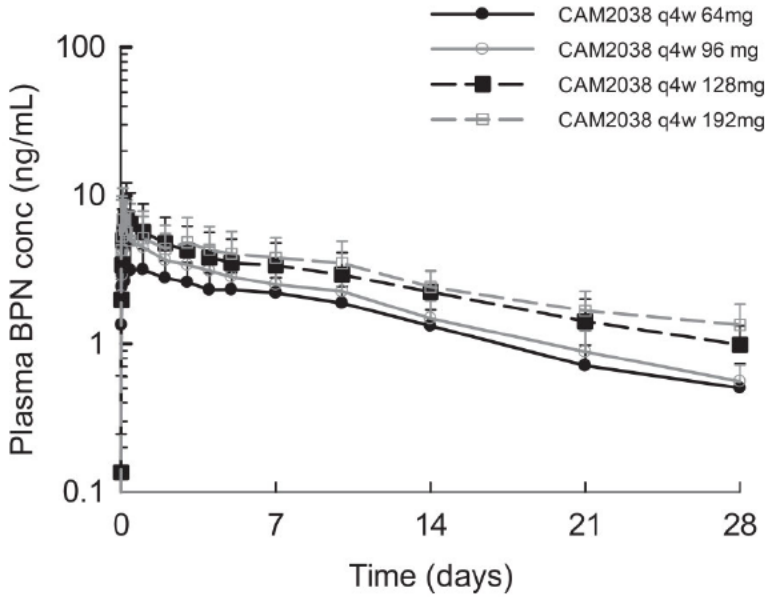


Figure 16: Plasma concentration-time profiles of Buprenorphine after single SC injection of CAM2038 q4w (mean ± SD)



Lastly, CAM2038 q1w is administered once weekly and CAM2038 q4w once monthly compared to the daily administered reference product Subutex (SL buprenorphine).

Reviewer's comments:

This fulfills the criterion of " The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product".

Reviewer's overall assessments:

The submitted information supports the extended release claim for CAM2038 q1w and CAM2038 q4w. The pharmacokinetic profiles of CAM2038 products show that there is no dose dumping, the steady-state performance is comparable to Subutex with less degree of fluctuation, the formulation provides consistent PK performance between individual dosage units, and the drug product has a less frequent dosing interval compared to Subutex.

Bridging of Formulations

Reviewer's Assessment:

The same CAM2038 q1w and CAM2038 q4w formulations have been used for the Phase 1 through Phase 3 of the clinical development program. The drug substance and drug product manufacturing sites were changed during development.

Table 9 and Table 10 show the comparison of product formulation, primary packaging and manufacturers used during development and for the final product for CAM2038 q1w and CAM2038 q4w, respectively.

Table 9: Details on product used during CAM2038 q1w development and on the final product

Clinical Study and Phase	Product Characteristics			
	CAM2038 q1w Composition	Container Closure	Drug Substance Manufacturer	Drug Product Manufacturer
HS-11-426 Phase 1	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	Vial	(b) (4)	(b) (4)
HS-13-487 Phase 1	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	Vial		
HS-07-307 Phase 1/2	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	Vial		
HS-13-478 Phase 2	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	PFS		Pii
HS-15-549 Phase 2	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	PFS		Pii
HS-11-421 Phase 3	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	PFS		Pii
HS-14-499 Phase 3	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	PFS		Pii
N/A Commercial	50 mg BUP/mL 10% w/w ethanol SPC/GDO 50/50	PFS		Pii

Vial (b) (4) glass vials (b) (4) rubber stoppers, aluminum crimp caps

PFS 1 mL long glass (b) (4) syringe with staked stainless steel 23G TW ½'' needle, rigid rubber needle shield, and (b) (4) elastomer (b) (4) plunger stopper

(b) (4)

Pii Pharmaceutics International Inc., 103 Beaver Court, Cockeysville, MD 21030, USA

Table 10: Details on product used during CAM2038 q4w development and on the final product

Clinical Study and Phase	Product Characteristics			
	CAM2038 q4w Composition	Container closure	Drug Substance Manufacturer	Drug Product Manufacturer
HS-13-487 Phase 1	356 mg buprenorphine/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and SPC/GDO in the weight ratio 40/60 to final volume	Vial	(b) (4)	(b) (4)
HS-15-549 Phase 2	356 mg buprenorphine/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and SPC/GDO in the weight ratio 40/60 to final volume	PFS		Pii
HS-11-421 Phase 3	356 mg buprenorphine/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and SPC/GDO in the weight ratio 40/60 to final volume	PFS		Pii
HS-14-499 Phase 3	356 mg buprenorphine/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and SPC/GDO in the weight ratio 40/60 to final volume	PFS		Pii
N/A Commercial	356 mg buprenorphine/mL, 30% w/w N-methyl-2-pyrrolidone (NMP) and SPC/GDO in the weight ratio 40/60 to final volume	PFS		Pii

Vial (b) (4) glass vials (b) (4) rubber stoppers, aluminum crimp caps
PFS 1 mL long glass (b) (4) syringe with staked stainless steel 23G TW ½'' needle, rigid rubber needle shield, and (b) (4) elastomer (b) (4) plunger stopper
(b) (4)
Pii Pharmaceutics International Inc., 103 Beaver Court, Cockeysville, MD 21030, USA

An IR was sent to the applicant on 8/8/2017 as follows:

Submit the comparative in vitro release data to bridge any formulation or manufacturing site change during your drug product development. Provide complete in vitro release profile data (n=12, individual, mean, %RSD, profiles) along with similarity factor comparison (f2) for your pre-change and post-change drug products.

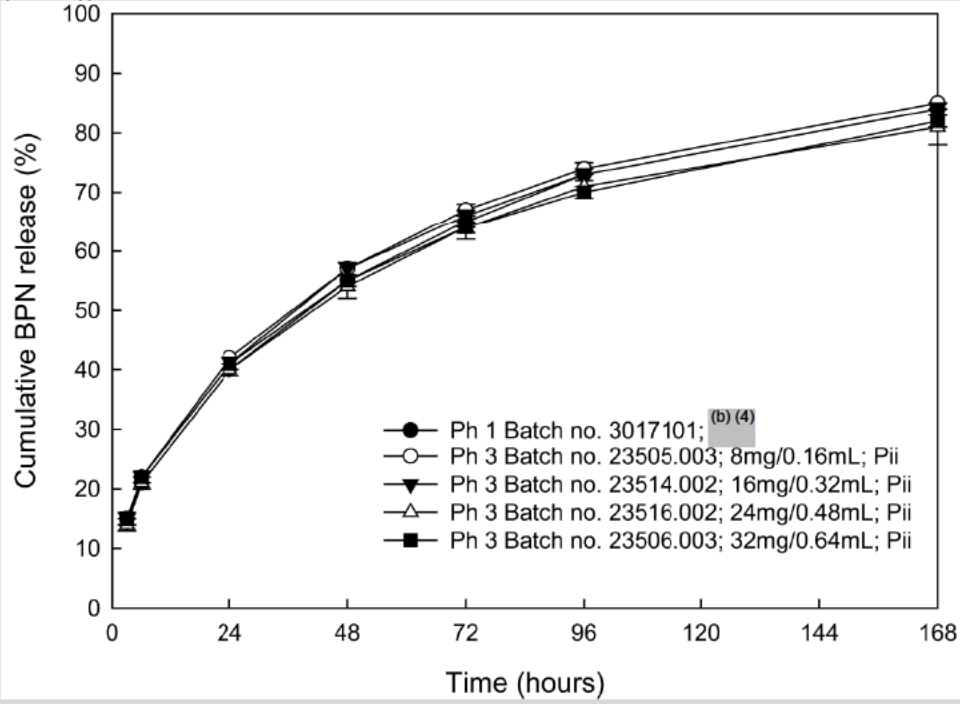
The applicant responded on 8/23/2017 with more detail information on bridging as follows.

CAM2038 q1w:

Comparative in vitro release mean profile for the batches used in the pharmacokinetic Phase 1 studies HS-11-426 and HS-13-487 (drug product in vial; manufacturer (b) (4) (b) (4)), the Phase 2 and 3 trials HS-13-478, HS-15-549, HS-11-421 and HS-14-499 (drug product in pre-filled syringes; manufacturer Pii, Cockeysville, USA) are provided in Figure 17. Fill volumes (pre-filled syringes) for Phase 3 batches are indicated in the legend.

Figure 17: Comparative in vitro release profiles of buprenorphine from CAM2038 q4w batches used for Phase 1 study HS-13-487 and for Phase 3 studies HS-11-421 and HS-14-499 (see Table 2 for product characteristics). The in vitro release profiles were obtained using the in vitro release assay based on Apparatus 1, data points represent mean values and error bars standard deviation

(n = 12)).



A comparative in vitro release test for bridging was performed by using the Phase 1 batch manufactured (b) (4) as reference. The applicant stated that the percent coefficient of variation at the later time points (24 and 48 hours) were between 8-15% and therefore the requirements for the use of mean data are not strictly fulfilled in all cases, the f2 was ≥ 63 for all respective profiles, and fulfills the guideline requirement of f2 > 50 (50-100), thus indicating a level of "sameness" of the profiles for the product manufactured at the respective sites.

Further information submitted on 8/23/2017 included the individual and mean values of in vitro release data for batch no. 3017101 used in Phase 1 studies HS-11-426 and HS-13-487 as shown in Table 11 (as reference), and in vitro release data for batch no. 23506.003 (32 mg/0.64 mL) in Table 12, no. 23516.002 (24 mg/0.48 mL) in Table 13, no. 23514.002 (16 mg/0.32 mL) in
Table 14, and 23505.003 (8 mg/0.16 mL) in Table 15 used in Phase 2 and 3 studies HS-13-478, HS-15-549, HS-11-421 and HS-14-499 (as test). The f2 values are all above 50.

Table 11: Individual and mean values of % BPN released for batch no. 3017101 provided in vials (CAM2038 q1w formulation), manufactured (b) (4) and used for Phase 1 studies HS-11-426 and HS-13-487.

Vessel	Time point (hours)						
	3	6	24	48	72	96	168
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean[1]	15	21	40	55	65	73	84
%RSD	3	2	2	2	2	2	1

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.

Table 12: Individual and mean values of % BPN released for batch no. 23506.003 (32 mg/0.64 mL) provided in pre-filled syringes (CAM2038 q1w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-13-478, HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)						
	3	6	24	48	72	96	168
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean[1]	15	22	41	55	64	70	82
%RSD	4	2	2	1	2	1	1
Similarity factor (f2)[2]	87						

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3017101 used as reference product.

Table 13: Individual and mean values of % BPN released for batch no. 23516.002 (24 mg/0.48 mL) provided in pre-filled syringes (CAM2038 q1w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-13-478, HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)						
	3	6	24	48	72	96	168
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Mean[1]	14	21	40	54	64	71	81
%RSD	7	5	4	4	2	3	4
Similarity factor (f2)[2]	87						

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3017101 used as reference product.

Table 14: Individual and mean values of % BPN released for batch no. 23514.002 (16 mg/0.32 mL) provided in pre-filled syringes (CAM2038 q1w), manufactured by Pii, Cockeysville, USA, and used

for Phase 2 and 3 studies HS-13-478, HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)						
	3	6	24	48	72	96	168
1	(b) (4)						
2							
3							
4							
5							
6							
Mean[1]	15	22	41	57	66	73	84
%RSD	3	3	2	2	2	2	1
Similarity factor (f2)[2]	92						

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3017101 used as reference product. Similarity factor calculated based on n = 6 for the indicated batch.

Table 15: Individual and mean values of % BPN released for batch no. 23505.003 (8 mg/0.16 mL) provided in pre-filled syringes (CAM2038 q1w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-13-478, HS-15-549, HS-11-421 and HS-14-499.

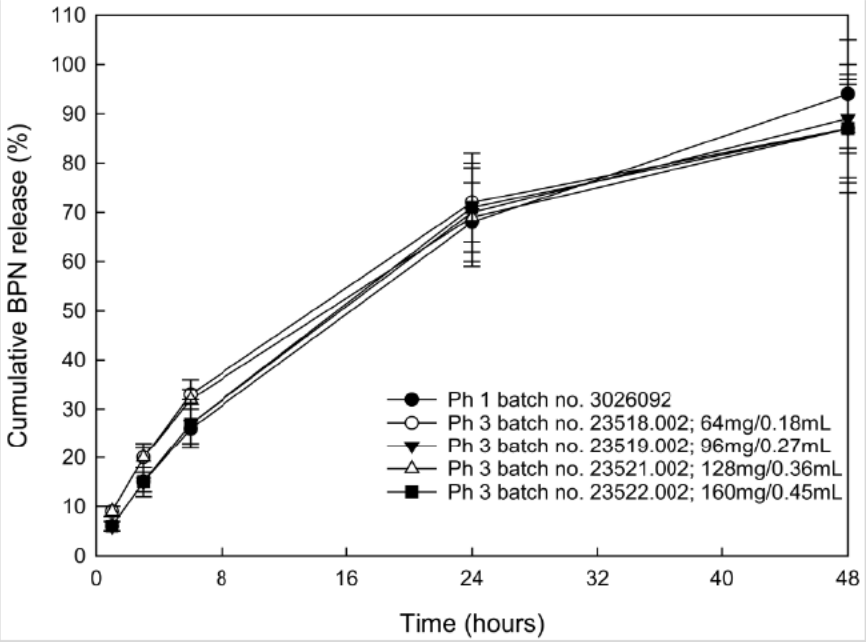
Vessel	Time point (hours)						
	3	6	24	48	72	96	168
1	(b) (4)						
2							
3							
4							
5							
6							
Mean[1]	15	22	42	57	67	74	85
%RSD	3	2	1	1	1	1	1
Similarity factor (f2)[2]	88						

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3017101 used as reference product. Similarity factor calculated based on n = 6 for the indicated batch.

CAM2038 q4w:

Comparative in vitro release data for the batches used in the pharmacokinetic Phase 1 study HS-13-487 (manufacturer (b) (4)), the Phase 2 and 3 trials HS-15-549, HS-11-421 and HS-14-499 (manufacturer Pii, Cockeysville, USA) are provided in Figure 18.

Figure 18: Comparative in vitro release profiles of buprenorphine from CAM2038 q4w batches used for Phase 1 study HS-13-487 and for Phase 3 studies HS-11-421 and HS-14-499. The in vitro release profiles were obtained using the in vitro release assay based on Apparatus 1, data points represent mean values and error bars standard deviation (n = 12)).



The applicant stated that although the percent coefficient of variation at the later time points (24 and 48 hours) were between 8-15% and therefore the requirements for the use of mean data are not strictly fulfilled in all cases, the f2 was ⩾ 63 for all respective profiles, and fulfils the guideline requirement of f2 > 50 (50-100), thus indicating a level of "sameness" of the profiles for the product manufactured at the respective sites.

Further information submitted on 8/23/2017 included the individual and mean values of in vitro release data in the pharmacokinetic Phase 1 study HS-13-487 (manufacturer (b) (4)) as shown in Table 16 (as reference), and in vitro release data representative batches used in the Phase 2 and 3 trials HS-15-549, HS-11-421 and HS-14-499 (manufacturer Pii, Cockeysville, USA) shown in Table 17-Table 20 (as test). The f2 values are all above 50.

Table 16: Individual and mean values of % BPN released for batch no. 3026092 provided in vials (CAM2038 q4w formulation), manufactured (b) (4) and used for Phase 1 study HS-13-487.

Vessel	Time point (hours)				
	1	3	6	24	48
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean[1]	6	15	26	68	94
%RSD	15	15	14	12	11

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.

Table 17: Individual and mean values of % BPN released for batch no. 23522.002 (160 mg/0.45 mL) provided in pre-filled syringes (CAM2038 q4w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)				
	1	3	6	24	48
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean[1]	6	15	27	71	87
%RSD	20	18	17	12	15
Similarity factor (f2)[2]	72				

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3026092 used as reference product.

Table 18: Individual and mean values of % BPN released for batch no. 23521.002 (128 mg/0.36 mL) provided in pre-filled syringes (CAM2038 q4w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)				
	1	3	6	24	48
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean[1]	9	20	32	69	87
%RSD	11	9	7	14	12
Similarity factor (f2)[2]	65				

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3026092 used as reference product.

Table 19: Individual and mean values of % BPN released for batch no. 23519.002 (96 mg/0.27 mL) provided in pre-filled syringes (CAM2038 q4w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)				
	1	3	6	24	48
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean[1]	6	15	27	70	89
%RSD	22	17	14	8	8
Similarity factor (f2)[2]	79				

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3026092 used as reference product.

Table 20: Individual and mean values of % BPN released for batch no. 23518.002 (64 mg/0.18 mL) provided in pre-filled syringes (CAM2038 q4w), manufactured by Pii, Cockeysville, USA, and used for Phase 2 and 3 studies HS-15-549, HS-11-421 and HS-14-499.

Vessel	Time point (hours)				
	1	3	6	24	48
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean[1]	9	20	33	72	87
%RSD	17	14	10	14	11
Similarity factor (f2)[2]	63				

1. Individual values shown without decimals whereas mean value calculated with more significant digits before rounding.
2. Batch no. 3026092 used as reference product.

Reviewer's comments: The f2 values calculated by this reviewer are the same as calculated by the applicant (shown in the tables from Table 12 to Table 15 for CAM2038 q1w and from Table 17 to Table 20 for CAM2038 q4w).

With f2 values exceed 50 for all in vitro release tests for both CAM2038 q1w and CAM2038 q4w, the in vitro release profiles of the current manufacturing process with (b) (4) *manufacturing site are considered similar to Pii (Pharmaceutics International Inc., 103 Beaver Court, Cockeysville, MD 21030, USA) manufacturing site. The manufacturing site change is acceptable.*

Biowaiver Request

Reviewer's Assessment: ***There is no Biowaiver requested for this NDA submission.***

Primary Biopharmaceutics Reviewer Names and Dates:
An-Chi Lu, Pharm.D., November 24, 2017
Kelly M. Kitchens, Ph.D., December 5, 2017; December 20, 2017

Secondary Biopharmaceutics Reviewer Names and Dates:
Kelly M. Kitchens, Ph.D., November 24, 2017
Tapash Ghosh, Ph.D., December 21, 2017

Kelly Kitchens

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Tapash Ghosh

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Date: 12/22/2017 09:19:49AM
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MICROBIOLOGY

Product Background:

ANDA: 210136

Drug Product Name / Strength: (b) (4) (buprenorphine) injection (50 mg/mL – weekly product; 356 mg/mL – monthly product)

Route of Administration: Subcutaneous injection

Applicant Name: Braeburn Pharmaceuticals Inc.

Manufacturing Site: Pharmaceutics International, Inc. (Pii)
103 Beaver Court
Cockeysville, MD 21030

Method of Sterilization: (b) (4)

Review Recommendation: The submission is not recommended for approval on the basis of sterility assurance.

Review Summary: The drug product is (b) (4)

List Submissions being reviewed: 7/19/2017, 08/23/2017, 10/06/2017, 10/30/2017, 11/09/2017, 11/29/2017, and 12/08/2017.

Concise Description Outstanding Issues Remaining: See "List of Deficiencies"

Supporting/Related Documents:

- **DMF # (b) (4)**
- **DMF # (b) (4) microbiology reviews D (b) (4) M04R01.doc (Inadequate), dated 03/27/2017, and D (b) (4) M04R02.doc (Adequate), dated 10/20/2017 (b) (4) (b) (4)**
- **DMF # (b) (4) microbiology review D1 (b) (4) M01R01.doc (Adequate), dated 05/27/2016. (b) (4)**

- **DMF # (b) (4)**
- **DMF # (b) (4) microbiology reviews (b) (4) mic1.doc (Inadequate), dated 07/16/2015; (b) (4) mic1a1.doc (Adequate (b) (4), Inadequate overall), dated 11/02/2015; and D (b) (4) M02.doc (Adequate), dated 07/26/2017 (b) (4) (b) (4) DMF # (b) (4) microbiology review D (b) (4) M02.doc (Adequate) (b) (4) (b) (4)**
- **DMF # (b) (4) (b) (4)**
- **DMF # (b) (4) microbiology review (b) (4) mic1a1.doc (Inadequate), dated 11/02/2015; (b) (4) mic1a2.doc (Adequate), dated 12/03/2015; and D (b) (4) M02.doc (Adequate), dated 07/26/2017 (b) (4)**
- **ANDA (b) (4)**
- **Microbiology review (b) (4) .doc (Adequate), dated 03/19/2016 (b) (4) (b) (4)**
- **ANDA (b) (4)**
- **ANDA (b) (4) microbiology review a (b) (4) mr01.doc (Adequate (b) (4) (b) (4) overall not recommended for approval), dated 10/28/2016.**

Remarks Section: Priority review has been granted. The applicant's submission dated 08/23/2017 is in response to the Agency's 08/08/2017 Information Request. Initially this review was performed by D. Schu. The 08/08/2017 IR was so substantial that the IR response is reviewed as part of the original NDA. The initial 08/08/2017 IR deficiencies are not included below. The applicant's response dated 10/06/2017 is in response to the Agency's Information Request dated 09/26/2017. The applicant provided responses to most of the microbiology deficiencies in their response dated 10/06/2017; however, the applicant was granted an extension until 10/30/2017 to respond to the deficiencies concerning (b) (4) The applicant's submission dated 11/09/2017 is in response to the Agency's Information Request dated 10/26/2017. The applicant's submission dated 11/29/2017 is in response to the Agency's Information Request dated 11/15/2017. The applicant's submission dated 12/08/2017 is in response to the Agency's Information Request dated 12/01/2017.

S Drug Substance - N/A, non-sterile.

P.1 Description of the Composition of the Drug Product

- Description of drug product – Sterile, yellowish to yellow clear solution filled into 1 mL long clear glass syringes. The drug product is formulated at 50 mg/mL for once weekly subcutaneous injection (CAM2038 Q1W-injection) and at 356 mg/mL for once monthly subcutaneous injection (CAM2038 Q4W-injection). Four different fill volumes (doses)

are provided for each drug strength. The fill volumes for the Q1W product are 0.16 mL, 0.32 mL, 0.48 mL, and 0.64 mL. The fill volumes for the Q4W product are 0.18 mL, 0.27 mL, 0.36 mL (b) (4) The drug products are extended-release products based on the proprietary FluidCrystal® (FC) injection depot technology.

- Drug product composition –

Composition of CAM2038 q1w Drug Product

Ingredient	Standard	Function	Composition (mg/dose)			
			8 mg/0.16 mL	16 mg/0.32 mL	24 mg/0.48 mL	32 mg/0.64 mL
Buprenorphine Base (BUP)	Ph. Eur.	API	8	16	24	32
Ethanol Anhydrous (EtOH)	USP	(b) (4)				
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					

Composition of CAM2038 q4w Drug Product

Ingredient	Standard	Function	Composition (mg/dose)			
			64 mg/0.18 mL	96 mg/0.27 mL	128 mg/0.36 mL	(b) (4)
Buprenorphine Base (BUP)	Ph. Eur.	API	64	96	128	
N-Methyl-2-Pyrrolidone (NMP)	USP				(b) (4)	
Soybean Phosphatidylcholine (SPC)	In-house					
Glycerol Dioleate (GDO)	In-house					

- Description of container closure system – All drug product presentations are filled into the container closure system summarized in the table below.

Component	Description	Manufacturer	DMF
Syringe	(b) (4) 1 mL long, glass (b) (4)	(b) (4)	DMF # (b) (4)
Needle	Staked 23G thin wall (TW) ½" stainless steel 3B		
Needle shield	Rigid Needle Shield (RNS), rubber formulation (b) (4) (b) (4) Grey		
Plunger stopper	(b) (4) 1 mL Long Plunger (b) (4) Gray with (b) (4) (b) (4) elastomer)	(b) (4)	DMF (b) (4)

The drug product-filled syringe is inserted into a safety device assembly. The safety device components are not in direct product contact and will not be reviewed here.

Reviewer's Assessment: Adequate
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

- **Container/Closure and Package Integrity**
(eCTD seq #0002: Section 3.2.P.2, *Container Closure System.pdf*, page 4; Section 3.2.P.3.5, *Process Validation and-or Evaluation (Q1W).pdf*, p. 4; Section 3.2.P.3.5, *Process Validation and-or Evaluation (Q1W).pdf*, p. 4)

The container / closure and package integrity information reviewed below includes the information provided in the submission dated 07/19/2017. The information also includes the applicant's 08/23/2017 response to the Agency's Information Request dated 08/08/2017.

Dye Ingress Method

CCIT was performed on the proposed container-closure system using the dye ingress method. (b) (4)

(b) (4)

Microbial Immersion Method

CCIT was also performed by the microbial immersion method. The submissions dated 07/19/2017 and 08/23/2017 do not provide the following information:

(b) (4)

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(b) (4)

Reviewer's Assessment: Adequate
The dye ingress visual inspection method's (b) (4) determined for the 0.16 mL fill CAM2038 q1w product and 0.18 mL fill CAM2038 q4w product is within the (b) (4) µl recommended range for CCIT. The same container-closure system is used for all CAM2038 q1w and q4w drug product presentations. The integrity of the container-closure system is adequately validated. The use of dye ingress by visual inspection for CCIT on stability will be reviewed in the post-approval stability section of the review below.

- **Antimicrobial Effectiveness Testing** - N/A. Both presentations of the drug product are labeled as a "single-use."

P.3 Manufacture
P.3.1 Manufacturers

Pharmaceutics International, Inc. (Pii), 103 Beaver Court, Cockeysville, MD 21030. Responsible for raw material testing, drug product manufacturing, and microbiological testing.

Pharmaceutics International, Inc. (Pii), 10819 Gilroy Rd, Hunt Valley, MD 21031. Responsible for QC testing, release to next assembly function, and stability testing.

(b) (4)
Responsible for container closure integrity testing of stability samples.

P. 3.3 Description of the Manufacturing Process and Process Controls

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Elizabeth Bearr

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John Arigo

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Date: 12/21/2017 11:00:42AM
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/s/

STEVEN A KINSLEY
12/22/2017