

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022410Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-410
Suboxone®
(buprenorphine and naloxone)
sublingual film 2 mg/0.5 mg and 8 mg/2 mg

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Reckitt Benckiser Pharmaceuticals Inc.

Indication: Suboxone is indicated for maintenance treatment of opioid dependence.

Presentation: The drug product is two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone). The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (2mg/0.5 mg/film) and a higher strength (8 mg/2 mg/film). Each strength will be available in 30 pouches per carton.

EER Status:	Recommendations:	acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	DMEPA-	Completed
	Biopharm-	N/A
	Microbiology -	N/A
	Pharm/toxicology -	N/A

Original Submission: 20-October-2008

Re-submissions: N/A

Post-Approval CMC PMC/PMR: None.

Background:

This NDA is submitted under 505b2. The drug product, Suboxone®, a soluble film designed for sublingual delivery, is a combination of buprenorphine and naloxone indicated for maintenance treatment of opioid dependence. Naloxone is an opioid receptor antagonist. Suboxone is an alternative to the currently marketed Suboxone® (buprenorphine/naloxone) sublingual tablet (NDA 20-733).

Drug Substances:

There are two drug substances for this NDA:

- **Buprenorphine hydrochloride** is manufactured the applicant. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Type II Drug Master File (DMF) 12412. DMF 12412 was reviewed and found satisfactory. The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition (b) (4), Specific Optical Rotation (b) (4), Residual Solvents (b) (4) by GC), Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity (b) (4) (b) (4) and any individual unspecified impurity can not exceed (b) (4) and their total no more than (b) (4). The specifications for Buprenorphine HCl comply and exceed those required by USP. A (b) (4) re-test period is established at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of (b) (4) subject to the material meeting the specification criteria.

Buprenorphine hydrochloride

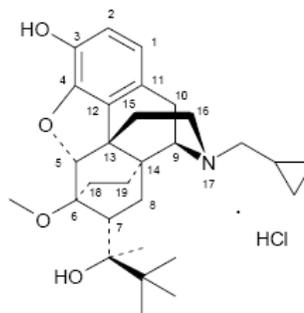
Laboratory Code: RX6029M.HCl

$C_{29}H_{41}NO_4 \cdot HCl$

MW: 467.6 (base) 504.1 (salt)

CAS Registry number: 53152-21-9

(2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride



- **Naloxone hydrochloride dihydrate**

There are two suppliers of naloxone hydrochloride dihydrate drug substance; the first supplier is (b) (4). CMC information is referred to their DMF (b) (4). DMF (b) (4) was reviewed and found satisfactory. The second supplier is (b) (4). CMC information is referred to their DMF (b) (4). DMF (b) (4) was reviewed and found satisfactory. The Reckitt Benckiser's naloxone HCl dihydrate purchasing specifications have been agreed with both suppliers. These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification (IR, TLC, Chloride), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition (b) (4), Optical Rotation (b) (4), Residual Solvents (b) (4) by GC), Assay (HPLC, titration), Ion

Chloride determination, Appearance of solution (visual), Loss on drying (gravimetric), and Purity (HPLC). Known impurities (b) (4) (b) (4) each NMT (b) (4) (b) (4) NMT (b) (4) and (b) (4) NMT (b) (4) Other (b) (4) impurities, including Ph Eur impurities (b) (4) each NMT (b) (4) and the total (known and unknown related substances) can not exceed (b) (4).

The supporting shelf-life support (b) (4) storage re-test period naloxone hydrochloride dihydrate.

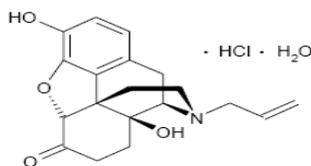
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGH

Naloxone hydrochloride dihydrate

$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$

MW: 399.9

CAS RN: 465-65-6 Naloxone.
357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate



4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate

Conclusion: The drug substances are satisfactory

Drug Product:

The manufacture process comprises (b) (4)

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone). Both dosage strengths have the same width and length, 0.875" x 0.5", but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties). Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each (b) (4) by HPLC), Dissolution (currently Q = (b) (4) in 7 minutes for buprenorphine and Q = (b) (4) in 7 minutes for naloxone), Moisture content uniformity (NMT (b) (4)), Microbial limits

(USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include (b) (4)

(b) (4) any Individual Unidentified Impurity NMT (b) (4) and their total can not exceed (b) (4) Purity requirements for Naloxone Related Substance include (b) (4)

(b) (4), and for (b) (4) each NMT (b) (4) Any Individual Unidentified Impurity NMT (b) (4) and the total of impurities can not exceed (b) (4)

Based on the provided stability data, 12 months of expiry dating is granted for the drug product (b) (4)

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief,
DPA I/ONDQA

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22410	----- ORIG 1	----- RECKITT BENCKISER PHARMACEUTICA LS INC	----- SUBOXONE (BUPRENORPHINE/NALOXONE) sublingual film

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

/s/

ALI H AL HAKIM
08/21/2009

NDA 22-410

Suboxone
(buprenorphine and naloxone)
Sublingual Film
2 mg/0.5 mg and 8 mg/2 mg

Reckitt Benckiser Pharmaceuticals Inc.

Xavier Ysern, PhD
ONDQA/ DPA I/ Branch II

Clinical Review Division: DAARP (HFD-170)

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Chemistry Review Data Sheet

- 1. NDA : 22-410
- 2. REVIEW #: 2
- 3. REVIEW DATE: 20-Aug-2009
- 4. REVIEWER: Xavier Ysern, PhD
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
--	--

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	20-Oct-2008
Amendments:	
0002	30-Oct-2008 (Proposed proprietary name Suboxone (b) (4))
0005	08-Dec-2008 (Environmental Assessment)
0009	03-Mar-2009 (Updated stability data)
0014	28-Apr-2009 (Change of secondary packaging facility)

7. NAME & ADDRESS OF APPLICANT:

Name: Reckitt Benckiser Pharmaceuticals Inc.
 Address: 10710 Midlothian Turnpike, Suite 430
 Richmond, VA23235
 Representative: Deborah C. Moffitt
 Manager, Regulatory Affairs Operations
 Telephone: 804 423-6970

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Suboxone
- b) Non-Proprietary Name (USAN): (buprenorphine and naloxone) sublingual film (established name)
- c) Code Name/# (ONDC only): --
- d) Chem. Type/Submission Priority:
 - Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of opioid dependence

11. DOSAGE FORM: Sublingual film

12. STRENGTH/POTENCY: 2 mg/0.5 mg and 8 mg/2 mg (buprenorphine/naloxone)

13. ROUTE OF ADMINISTRATION: Sublingual (b) (4) route

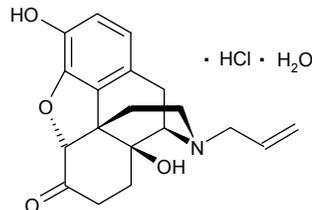
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Naloxone hydrochloride dihydrate

C₁₉H₂₁NO₄·HCl·2H₂O

MW: 399.9

CAS RN: 465-65-6 Naloxone.
357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate



4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate

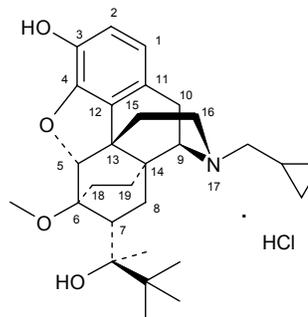
Buprenorphine hydrochloride

Laboratory Code: RX6029M.HCl

C₂₉H₄₁NO₄·HCl

MW: 467.6 (base) 504.1 (salt)

CAS Registry number: 53152-21-9



(2*S*)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
Type II		(b) (4)				
12412	Reckitt Benckiser Healthcare (UK) Ltd.	Buprenorphine HCl	1	Adequate	05-Feb-2009	CMC Review # 9
		(b) (4)	1	Adequate	21-Jan-2009	CMC Review # 4
		(b) (4)	1	Adequate	24-Feb-2009	CMC Review # 1
Type IV	(b) (4)	(b) (4) lime flavor (b) (4)	4	Adequate		LOA 09-Sep-2008
		White Ink (b) (4)	4	Adequate		LOA 17-Sep-2007

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF. 3 – Reviewed previously and no revision since last review.

5 – Authority to reference not granted. 6 – DMF not available.

4 – Sufficient information in application

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application #	Description
NDA	20-732	Subutex (Buprenorphine) Tablets 2 mg and 8 mg
NDA	20-733	Suboxone (Buprenorphine and Naloxone) sublingual tablet 2/0.5 mg and 8/2 mg

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--		
EES	Acceptable recommendation	20-Aug-2009	
Pharm/Tox	--		
Biopharm	--		
Labeling	OSE does not object the use of the tradename Suboxone. The drug product should be referred as "Suboxone (Buprenorphine and Naloxone) sublingual film" throughout all labels and labeling documentation.	08-Aug-2009	Multidisciplinary
Methods Validation	Revalidation by Agency laboratories is not recommended		Part of this review
EA	Acceptable		Part of this review
Microbiology	--		

The Chemistry Review for NDA 22410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the CMC point of view, the application is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product, Suboxone (b) (4) a soluble film designed for sublingual delivery, is a combination of buprenorphine and naloxone indicated for maintenance treatment of opioid dependence. Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Naloxone is an opioid receptor antagonist. Suboxone (b) (4) is an alternative to the currently marketed Suboxone® (buprenorphine/naloxone) sublingual tablet (NDA20-733).

- Drug Substance(s)

Buprenorphine hydrochloride

Buprenorphine hydrochloride, chemical name (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride, has the molecular formula C₂₉H₄₁NO₄·HCl and a molecular weight of 504.10 g/mol. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

Buprenorphine, the active component of buprenorphine hydrochloride, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine is a thebaine (paramorphine an opiate alkaloid) derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Buprenorphine also has very high binding affinity for the μ receptor such that opioid receptor antagonists (e.g. naloxone) only partially reverse its effects.

Buprenorphine hydrochloride is manufactured by the applicant at their facility, “Fine Chemical Plant” (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited’ Type II Drug Master File (DMF) 12412.

The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition (b) (4), Specific Optical Rotation (b) (4), Residual Solvents (b) (4) by GC, Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity (b) (4) and any individual unspecified impurity can not exceed (b) (4) and their total no more than (b) (4) Reckitt Benckiser’s specifications for Buprenorphine HCl comply and exceed those required by USP.

Bulk (b) (4) drug substance is stored in (b) (4). A (b) (4) re-test data is applied at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of (b) (4) subject to the material meeting the specification criteria.

Naloxone hydrochloride dihydrate

Naloxone hydrochloride dihydrate, chemical name 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate, has the molecular formula C₁₉H₂₁NO₄·HCl·2H₂O and a molecular weight of 399.87 g/mol. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol; practically insoluble in toluene and ether.

Naloxone, the active component of naloxone hydrochloride dihydrate, is a potent antagonist at mu-opioid receptors and produces opioid withdrawal effects in individuals physically dependent on full opioids. Naloxone is included in the Suboxone (b) (4) formulation to deter users from diverting its use to intravenous injection by producing opioid antagonist effects of short duration in subjects dependent on full opioid agonists.

There are two suppliers of naloxone hydrochloride dihydrate drug substance, (b) (4) and (b) (4). (b) (4) naloxone hydrochloride dihydrate is manufactured in their (b) (4) facility. The pertinent CMC information is referred to their proprietary Type II DMF (b) (4). (b) (4) naloxone hydrochloride dihydrate is manufactured at their facility in (b) (4). The CMC information is referred to their proprietary Type II DMF (b) (4).

The Reckitt Benckiser's naloxone HCl dihydrate purchasing specifications have been agreed with both (b) (4) (main drug substance supplier) and (b) (4) (alternate supplier). These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification (IR, TLC, Chloride), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition (b) (4), Optical Rotation (b) (4), Residual Solvents (b) (4) by GC), Assay (HPLC, titration), Ion Chloride determination, Appearance of solution (visual), Loss on drying (gravimetric), and Purity (HPLC). Known impurities (b) (4). (b) (4) NMT (b) (4). Other impurities, including Ph Eur impurities (b) (4) each NMT (b) (4) and the total (known and unknown related substances) can not exceed (b) (4) %.

Naloxone hydrochloride dihydrate is supplied by (b) (4) in (b) (4) containers and in (b) (4) containers by (b) (4). The supporting shelf-life given by the suppliers exceed the (b) (4) storage period before re-test applied by Reckitt Benckiser.

• Drug Product

Suboxone (b) (4) is a pale orange soluble film strip imprinted with a logo identifying the product and strength in white ink designed to provide immediate release of buprenorphine and naloxone in a 4:1 w/w ratio sublingually.

In addition to the active components buprenorphine and naloxone, the film contains polyethylene oxide (b) (4), hydroxypropyl methylcellulose (b) (4), maltitol (b) (4), acesulfame potassium (b) (4), lime flavor (b) (4), citric acid (b) (4), sodium citrate (b) (4), FD&C yellow # 6 (colorant) and white ink (print ink). All excipients, with the exception of lime flavor, FD&C yellow # 6 and white ink, meet compendial requirements. The lime flavor, (b) (4) Lime Flavor (b) (4), is the same used in approved Suboxone Tablets (NDA 20-733), complies with food additives as per 21 CFR §172.510. FD&C Yellow # 6 is a FDA certified colorant permitted for food use as per 21 CFR §74.706, also

employed in Suboxone Tablets. The ink is an edible grade supplied by (b) (4) and all components are compendial.

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone), referred as lower and higher strengths respectively. Both dosage strengths have the same width and length, 0.875" x 0.5", but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties).

The manufacture process comprises (b) (4)

Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each (b) (4) by HPLC), Dissolution (currently Q = (b) (4) in 7 minutes for buprenorphine and Q = (b) (4) in 7 minutes for naloxone), Moisture content uniformity (NMT (b) (4)), Microbial limits (USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include (b) (4) any Individual Unidentified Impurity NMT (b) (4) and their total can not exceed (b) (4) Purity requirements for Naloxone Related Substance include (b) (4) and for (b) (4) each NMT (b) (4) Any Individual Unidentified Impurity NMT (b) (4) and the total of impurities can not exceed (b) (4)

Both buprenorphine and naloxone are susceptible to radical oxidative degradation processes. The degradation products forming in Suboxone (b) (4) appear consistent with those observed in the sublingual tablets, although there is some difference in their relative rates of formation. Based on the provided stability data, a 12 months expiration dating is granted.

The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (buprenorphine/naloxone 2 mg/0.5 mg/strip) 30 pouches per carton (NDC 12496-1402-3), and a higher strength (buprenorphine/naloxone 8 mg/2 mg/strip; content expressed in terms of free base) 30 pouches per carton (NDC 12496-1408-3). The product is recommended to be stored at room temperature, "Store at 25 °C (77 °F), excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]", and advised to store it out of sight and reach of children.

B. Description of How the Drug Product is Intended to be Used

Suboxone (b) (4) is indicated for maintenance treatment of opioid dependence. The drug product is designed to deliver buprenorphine by the sublingual (b) (4) route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA20-733).

C. Basis for Approvability or Not-Approval Recommendation

The pending issue, an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance, has been satisfactorily resolved (EER summary report, dated 20-Aug-2009, is attached).

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for Naloxone Hydrochloride Dihydrate, and DMF 12412 for Buprenorphine Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments.

From the CMC standpoint NDA 22-410 is recommended for approval.

III. Administrative

A. Reviewer's Signature	Xavier Ysern, PhD	Review Chemist/ ONDQA/ DPA I/ Branch II
B. Endorsement Block	Ali Al-Hakim, PhD	Branch Chief/ ONDQA/ DPA I/ Branch II
C. CC Block	Matthew Sullivan	Project Manager/ OND/ ODE II/ DAARP

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22410	ORIG 1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE)
NDA 22410	ORIG 1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE)

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/s/

XAVIER J YSERN
08/20/2009

ALI H AL HAKIM
08/20/2009

NDA 22-410

Suboxone ^{(b) (4)} *
(buprenorphine and naloxone) sublingual film
2 mg/0.5 mg and 8 mg/2 mg

Reckitt Benckiser Pharmaceuticals Inc.

Xavier Ysern, PhD
Office of New Drug Quality Assurance

Division of Analgesia, Anesthesia, and Rheumatology Products (HFD-170)

* The originally proposed tradename is used throughout the review. The proposed tradename is not acceptable.

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Chemistry Review Data Sheet

1. NDA : 22-410
2. REVIEW #: 1
3. REVIEW DATE: 06-Jul-2009
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
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6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	20-Oct-2008
Amendments:	
0002	30-Oct-2008 (Proposed proprietary name Suboxone (b) (4))
0005	08-Dec-2008 (Environmental Assessment)
0009	03-Mar-2009 (Updated stability data)
0014	28-Apr-2009 (Change of secondary packaging facility)

7. NAME & ADDRESS OF APPLICANT:

Name: Reckitt Benckiser Pharmaceuticals Inc.
 Address: 10710 Midlothian Turnpike, Suite 430
 Richmond, VA23235
 Representative: Deborah C. Moffitt
 Manager, Regulatory Affairs Operations
 Telephone: 804 423-6970

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Suboxone (b) (4) (proposed by the applicant)
- b) Non-Proprietary Name (USAN): (buprenorphine and naloxone) sublingual film (established name)
- c) Code Name/# (ONDC only): --
- d) Chem. Type/Submission Priority:
- Chem. Type: 4
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of opioid dependence

11. DOSAGE FORM: Sublingual film

12. STRENGTH/POTENCY: 2 mg/0.5 mg and 8 mg/2 mg (buprenorphine/naloxone)

13. ROUTE OF ADMINISTRATION: Sublingual (b) (4) route

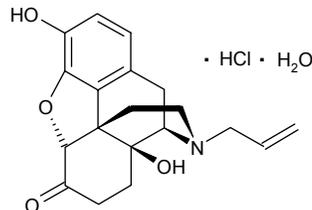
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Naloxone hydrochloride dihydrate

C₁₉H₂₁NO₄·HCl·2H₂O

MW: 399.9

CAS RN: 465-65-6 Naloxone.
357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate



4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate

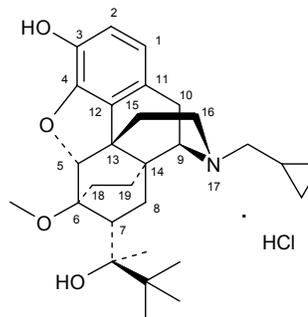
Buprenorphine hydrochloride

Laboratory Code: RX6029M.HCl

C₂₉H₄₁NO₄·HCl

MW: 467.6 (base) 504.1 (salt)

CAS Registry number: 53152-21-9



(2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
Type II		(b) (4)	1	Adequate	05-Feb-2009	CMC Review # 9
12412	Reckitt Benckiser Healthcare (UK) Ltd	Buprenorphine HCl	1	Adequate	21-Jan-2009	CMC Review # 4
		(b) (4)	1	Adequate	24-Feb-2009	CMC Review # 1
	(b) (4)	(b) (4) 1 lime flavor (b) (4)	4	Adequate		LOA 09-Sep-2008
		White Ink (b) (4)	4	Adequate		LOA 17-Sep-2007

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF. 3 – Reviewed previously and no revision since last review.

5 – Authority to reference not granted. 6 – DMF not available.

4 – Sufficient information in application

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application #	Description
NDA	20-732	Subutex (Buprenorphine) Tablets 2 mg and 8 mg
NDA	20-733	Suboxone (Buprenorphine and Naloxone) sublingual tablet 2/0.5 mg and 8/2 mg

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--		
EES	Pending		
Pharm/Tox	--		
Biopharm	--		
Labeling	Pending		
Methods Validation	Revalidation by Agency laboratories is not recommended		Part of this review
EA	Acceptable		Part of this review
Microbiology	--		

The Chemistry Review for NDA 22410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the CMC point of view, the application is recommended for approval pending an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug product, Suboxone (b) (4), a soluble film designed for sublingual delivery, is a combination of buprenorphine and naloxone indicated for maintenance treatment of opioid dependence. Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Naloxone is an opioid receptor antagonist. Suboxone (b) (4) is an alternative to the currently marketed Suboxone® (buprenorphine/naloxone) sublingual tablet (NDA20-733).

- Drug Substance(s)

Buprenorphine hydrochloride

Buprenorphine hydrochloride, chemical name (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride, has the molecular formula C₂₉H₄₁NO₄·HCl and a molecular weight of 504.10 g/mol. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

Buprenorphine, the active component of buprenorphine hydrochloride, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine is a thebaine (paramorphine an opiate alkaloid) derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Buprenorphine also has very high binding affinity for the μ receptor such that opioid receptor antagonists (e.g. naloxone) only partially reverse its effects.

Buprenorphine hydrochloride is manufactured by the applicant at their facility, "Fine Chemical Plant" (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the chemistry, manufacturing, and controls (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited' Type II Drug Master File (DMF) 12412.

The specifications for Buprenorphine HCl Drug Substance include Physical Description (visual), Identification (NIR, UV, Chlorides), pH (aqueous suspension), Water (Karl Fischer), Residue on Ignition (b) (4), Specific Optical Rotation (b) (4), Residual Solvents (b) (4) by GC, Assay (HPLC, titration), Ion Chloride determination, Purity (HPLC) and Particle Size Distribution. Each known impurity ((b) (4)) and any individual unspecified impurity can not exceed (b) (4) and their total no more than (b) (4) Reckitt Benckiser's specifications for Buprenorphine HCl comply and exceed those required by USP.

Bulk (b) (4) drug substance is stored in (b) (4). A (b) (4) re-test data is applied at the time of manufacture and the expiration date is extended in six monthly units up to a shelf life of (b) (4) subject to the material meeting the specification criteria.

Naloxone hydrochloride dihydrate

Naloxone hydrochloride dihydrate, chemical name 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate, has the molecular formula C₁₉H₂₁NO₄·HCl·2H₂O and a molecular weight of 399.87 g/mol. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol; practically insoluble in toluene and ether.

Naloxone, the active component of naloxone hydrochloride dihydrate, is a potent antagonist at mu-opioid receptors and produces opioid withdrawal effects in individuals physically dependent on full opioids. Naloxone is included in the Suboxone (b) (4) formulation to deter users from diverting its use to intravenous injection by producing opioid antagonist effects of short duration in subjects dependent on full opioid agonists.

There are two suppliers of naloxone hydrochloride dihydrate drug substance, (b) (4) (b) (4) naloxone hydrochloride dihydrate is manufactured in their (b) (4) facility. The pertinent CMC information is referred to their proprietary Type II DMF (b) (4) DMF (b) (4) naloxone hydrochloride dihydrate is manufactured at their facility in (b) (4). The CMC information is referred to their proprietary Type II DMF (b) (4).

The Reckitt Benckiser's naloxone HCl dihydrate purchasing specifications have been agreed with both (b) (4) (main drug substance supplier) and (b) (4) (alternate supplier). These specifications, which comply and exceed those required by both USP and Ph Eur, include Physical Description (visual), Identification ((b) (4)), Acidity or alkalinity (titrimetric), Water content (Karl Fischer), Residue on Ignition (b) (4), Optical Rotation (b) (4), Residual Solvents (b) (4), Assay (HPLC, titration), Ion Chloride determination, Appearance of solution (visual), Loss on drying (b) (4), and Purity (HPLC). Known impurities (b) (4). Other impurities, including Ph Eur impurities (b) (4) each NMT (b) (4) and the total (known and unknown related substances) can not exceed (b) (4) %.

Naloxone hydrochloride dihydrate is supplied by (b) (4) in (b) (4) containers and in (b) (4) containers by (b) (4). The supporting shelf-life given by the suppliers exceed the (b) (4) storage period before re-test applied by Reckitt Benckiser.

• Drug Product

Suboxone (b) (4) is a pale orange soluble film strip imprinted with a logo identifying the product and strength in white ink designed to provide immediate release of buprenorphine and naloxone in a 4:1 w/w ratio sublingually.

In addition to the active components buprenorphine and naloxone, the film contains polyethylene oxide (b) (4), hydroxypropyl methylcellulose (b) (4), maltitol (b) (4), acesulfame potassium (b) (4), lime flavor (b) (4), citric acid (b) (4), sodium citrate (b) (4), FD&C yellow # 6 (colorant) and white ink (print ink). All excipients, with the exception of lime flavor, FD&C yellow # 6 and white ink, meet compendial requirements. The lime flavor, (b) (4) Lime Flavor (b) (4) is the same used in approved Suboxone Tablets (NDA 20-733), complies with food additives as per 21 CFR §172.510. FD&C Yellow # 6 is a FDA certified colorant permitted for food use as per 21 CFR §74.706, also

employed in Suboxone Tablets. The ink is an edible grade supplied by (b) (4) and all components are compendial.

The drug product is manufactured in two different film formulations: 2 mg/0.5 mg and 4 mg/2 mg (buprenorphine/naloxone), referred as lower and higher strengths respectively. Both dosage strengths have the same width and length, 0.875" x 0.5", but differ in weight, 40 mg for the lower strength and 50 mg for the higher. Although both formulations share the same excipients, their composition is different. Those differences in formulation, obtained during product development, assure that each formulation has the desired properties (flexibility, disintegration and pharmacokinetic properties).

The manufacture process comprises (b) (4)

Drug product specifications include Appearance (visual), Identification (HPLC), Assay (buprenorphine and naloxone each (b) (4) by HPLC), Dissolution (currently Q = (b) (4) in 7 minutes for buprenorphine and Q = (b) (4) in 7 minutes for naloxone), Moisture content uniformity (NMT (b) (4) Microbial limits (USP<905>), and Purity (HPLC). Purity requirements for Buprenorphine Related Substances include (b) (4)

(b) (4) any Individual Unidentified Impurity NMT (b) (4) and their total can not exceed (b) (4) Purity requirements for Naloxone Related Substance include (b) (4)

(b) (4) Any Individual Unidentified Impurity NMT (b) (4) and the total of impurities can not exceed (b) (4)

Both buprenorphine and naloxone are susceptible to radical oxidative degradation processes. The degradation products forming in Suboxone (b) (4) appear consistent with those observed in the sublingual tablets, although there is some difference in their relative rates of formation. Based on the provided stability data, a 12 months expiration dating is granted.

The drug product is supplied in individual child-resistant polyester/foil laminated pouches available in a lower strength (buprenorphine/naloxone 2 mg/0.5 mg/strip) 30 pouches per carton (NDC 12496-1402-3), and a higher strength (buprenorphine/naloxone 8 mg/2 mg/strip; content expressed in terms of free base) 30 pouches per carton (NDC 12496-1408-3). The product is recommended to be stored at room temperature, "Store at 25 °C (77 °F), excursions permitted to 15 - 30 °C (59 - 86 °F) [see USP Controlled Room Temperature]", and advised to store it out of sight and reach of children.

B. Description of How the Drug Product is Intended to be Used

Suboxone (b) (4) is indicated for maintenance treatment of opioid dependence. The drug product is designed to deliver buprenorphine by the sublingual (b) (4) route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA20-733).

C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance ((b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for Naloxone Hydrochloride Dihydrate, and DMF 12412 for Buprenorphine Hydrochloride) and drug product manufactured, tested and packaged in accordance with the procedures and recommendation given in the original submission and pertinent amendments. NDA 22-410 is recommended for approval from the standpoint of chemistry, manufacturing and controls (CMC) pending an acceptable recommendation for the overall cGMP status of the manufacturing, testing and packaging facilities by the Office of Compliance.

III. Administrative

A. Reviewer's Signature	Xavier Ysern, PhD	Review Chemist/ ONDQA/ DPA I/ Branch II
B. Endorsement Block	Ali Al-Hakim, PhD	Branch Chief/ ONDQA/ DPA I/ Branch II
C. CC Block	Matthew Sullivan	Project Manager/ OND/ ODE II/ DAARP

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

/s/

Xavier Ysern
7/6/2009 06:00:56 PM
CHEMIST

Ali Al-Hakim
7/7/2009 11:16:05 AM
CHEMIST

Initial Quality Assurance (IQA)

NDA 22-410

Sponsor: Reckitt Benckiser Pharmaceuticals Inc.
Proposed trade name: Suboxone (b) (4)
Non-proprietary name: Buprenorphine and naloxone soluble film (proposed).
Indication: Treatment of opioid dependence.

This NDA is a 505(b)(1) application but relies partially on the information previously submitted to their other two NDAs, Subutex (Buprenorphine) Tablets 2 and 8 mg (NDA 20-732) and Suboxone (Buprenorphine and Naloxone) Sublingual Tablets 2 mg/0.5 mg and 8 mg/2 mg.

Key Dates

Letter date: 20-Oct-2008
Stamp date: 21-Oct-2008
Filing meeting date: 03-Dec-2008
Filing decision: 20-Dec-2008 (Day 60)
Mid cycle date: 21-Mar-2009 (end of Month 5)
W/U: 21-Jun-2009 (end Month 8)
1ry and 2ry reviews due: 21-Jun-2009
PDUFA Date: 21-Aug-2009

Drug Substance

The drug product, Suboxone® (b) (4) (buprenorphine and naloxone soluble film), contains two active components, buprenorphine (formulated into the drug product as buprenorphine hydrochloride) and naloxone (formulated into the drug product as naloxone hydrochloride dihydrate).

- Buprenorphine hydrochloride

Buprenorphine, a semisynthetic opioid, is a thebaine derivative with powerful analgesia approximately twenty-five to forty times as potent as morphine. Its analgesic effect is due to partial agonist activity at μ -opioid receptors. Buprenorphine is also a κ -opioid receptor antagonist.

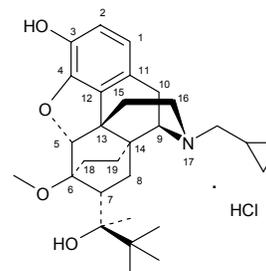
Buprenorphine hydrochloride is manufactured by the applicant at their's facility, "Fine Chemical Plant" (Reckitt Benckiser Healthcare Limited), located in Hull, United Kingdom. The information on the quality, chemistry, and manufacturing (CMC) for buprenorphine hydrochloride drug substance is referred to Reckitt Benckiser Healthcare (UK) Limited's Type II Drug Master File (DMF) 12412. Buprenorphine hydrochloride is sparingly soluble in water, freely soluble in methanol, soluble in ethanol and practically insoluble in cyclohexane. Its chemical name, structure, empirical formula and molecular weight are given below.

Laboratory Code: RX6029M·HCl

$C_{29}H_{41}NO_4 \cdot HCl$

MW: 467.6 (base) 504.1 (salt)

CAS Registry number (CAS RN): 53152-21-9



(2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride
(2S)-2-[-(5R,6R,7R,14S)-9 α -cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol hydrochloride

The specifications for Buprenorphine HCl Drug Substance are shown in Table S-1 (details on the analytical procedures and corresponding validation are referred to DMF 12412).

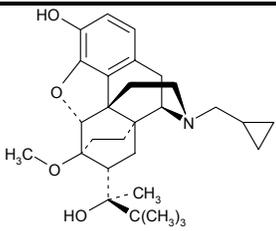
Table S-1. Reckitt Benckiser Specifications for Buprenorphine HCl

<i>Test</i>	<i>Acceptance criteria</i>	<i>Test Method Reference</i>
Physical description	White to off-white powder, free from visible contamination	65541 - TM EU
Identification	Shall be positive	65542 - TM EU
(b) (4)	(b) (4)	23455 - TM EU
(b) (4)	(b) (4)	23456 - TM EU
Water by Karl Fischer	(b) (4)	23460 - TM EU
(b) (4)	(b) (4)	23458 - TM EU
Residue on Ignition	(b) (4)	23462 - TM EU
Specific optical rotation	(b) (4)	23461 - TM EU
Impurities ^a	(b) (4)	23456 - TM EU
(b) (4)	(b) (4)	23465 - TM EU
Any individual unspecified impurity:		
Total:	(b) (4)	23463 - TM EU
Assay by HPLC	(b) (4)	23466 - TM EU
Assay by titration	(b) (4)	23464 - TM EU
Particle size	(b) (4)	65224 - TM EU

^a Chemical Structures shown in Table S-2.

^b With reference to the solvent-free anhydrous material.

Table S-2. Chemical Structures of Buprenorphine and Known Impurities

 <p>RX6029M (Buprenorphine)</p>	(b) (4)
(b) (4)	(b) (4)

The specifications for Buprenorphine HCl, meet compendial requirements, and are stricter than those required by USP. A comparison of the Reckitt Benckiser Healthcare (UK) Ltd. (Reckitt) specifications and USP monograph for buprenorphine hydrochloride (buprenorphine) is presented in Table S-3.

Table S-3. Buprenorphine HCl Drug Substance Specifications Comparison

<i>Reckitt Benckiser Specification</i>	<i>USP Monograph</i>
Physical description White to off white powder, free from visible contamination.	Physical description White to off white powder, free from visible contamination
Identification:	Identification:
· (b) (4)	A. IR absorption
· IR, (b) (4)	B. To 0.5ml of a solution of buprenorphine HCl in methanol containing 50mg per mL add 0.2mL of a freshly prepared solution (1 in 10) of potassium ferricyanide TS and 0.5mL of ferric chloride TS: a blue color appears immediately
	C. A solution (1 in 100) meets the requirements of the tests for chloride <191>
pH (b) (4) 4.0 – 6.0	pH <791>: between 4.0 and 6.0 in a solution containing 10 mg per mL
Water by Karl Fischer NMT (b) (4)	Water Method I <921>: not more than 0.1%
(b) (4) NMT (b) (4)	Residual Solvents <467>: meets the requirements
Residue on Ignition NMT (b) (4)	Residue on Ignition <281>: not more than 0.1%
Specific Optical Rotation (b) (4)	Specific Optical Rotation <781S>: between –92 ° and –98 ° Test solution: 20mg per mL, in methanol
(b) (4) –92 ° and -98 ° (b) (4)	Chromatographic purity (HPLC)
Related substances (HPLC) (b) (4)	Any individual impurity: NMT 0.25 %
(b) (4)	Sum of all impurities: NMT 0.65 %
Any individual unspecified impurity: NMT (b) (4)	
Total: NMT (b) (4)	
Assay: Titrimetric 98.5 % to 101.0 % (anhydrous) ^a	Assay: Titrimetric 98.5 % to 101.0 % (anhydrous)
Additional In-House Tests	
Appearance (b) (4)	
Shall be clear, colorless and essentially free from particles	
Assay by HPLC (b) (4) (anhydrous) ^a	
(b) (4) (b) (4) %	
Particle Size (b) (4) w/w minimum	

^a = with reference to the solvent-free anhydrous material.

- *Buprenorphine hydrochloride drug substance manufactured by Reckitt Benckiser Healthcare (UK) Ltd. according to the procedures and control given in DMF 12421 is used in the manufacture of the drug products of approved Subutex (buprenorphine) tablets (NDA 20-732 and Suboxone (buprenorphine and soloxone) sublingual tablets.*
- *DMF 12412 has been reviewed and deemed acceptable (2002).*
- *The last update to DMF 12412 is the 2008 update (Report No. RC080087) and no significant changes are reported. Therefore, **buprenorphine HCl drug substance manufactured and controlled as described in DMF 12412 is acceptable** for use in the manufacture of the drug product Suboxone® (b) (4) (buprenorphine and naloxone soluble film).*

- Naloxone hydrochloride dihydrate

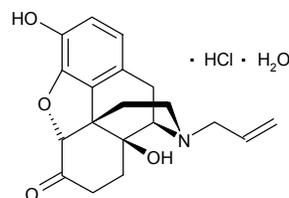
Naloxone is a potent antagonist at the μ -opioid and κ -opioid receptors and produces opioid withdrawal effects in opioid dependent subjects. Naloxone is poorly bioavailable by the sublingual route but has an increased bioavailability when administered by injection. Naloxone was added to Suboxone in an effort to dissuade patients from grinding up the Suboxone tablet and using it as part of a combination of opiates that the user would inject into their body.

Naloxone is manufactured by a number of opioid manufacturers including (b) (4), the supplier of naloxone hydrochloride dihydrate drug substance, and the alternate supplier (b) (4). The information on the quality, chemistry, and manufacturing (CMC) for naloxone hydrochloride dihydrate drug substance is referred to Type II DMFs (b) (4) and (b) (4).

Naloxone hydrochloride dehydrate, a white or almost white crystalline powder, is freely soluble in water, soluble in alcohol and practically insoluble in toluene. Its chemical name, structure, empirical formula and molecular weight are given below.

$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$
MW: 399.9

CAS RN: 465-65-6 Naloxone.
357-08-4 Naloxone hydrochloride anhydrous
51481-60-8 Naloxone hydrochloride dihydrate



4,5 α -Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride

Drug substance supplied by (b) (4) is manufactured at their (b) (4) plant, according to their confidential Type II DMF (b) (4) supplied drug substance is manufactured at their (b) (4) plant, where naloxone hydrochloride dihydrate is (b) (4).

There is both a USP monograph and European Pharmacopoeial (Ph.Eur.) monograph for naloxone. The Reckitt Benckiser's purchasing specifications complies fully with both but with a more stringent, ICH3 compliant, specification for the levels of impurities. In particular, (b) (4) a synthesis impurity in naloxone has an associated structural alert (b) (4) and has been shown to be weakly clastogenic. As a consequence it is controlled to a limit of (b) (4) a level accepted by the Agency, and below the guideline limit for genotoxic impurities.

The Reckitt Benckiser's naloxone HCl dihydrate purchasing specifications, shown in Table S-4, have been agreed with both (b) (4) (main drug substance supplier) and (b) (4) (alternate supplier).

- Naloxone HCl dihydrate manufactured by (b) (4) according to the procedures and control given in DMF (b) (4) is used in the manufacture of the approved drug Suboxone (buprenorphine and soloxone) sublingual tablets.
- DMF (b) (4) has been reviewed and deemed acceptable (2002).
- The last update to DMF (b) (4) is the 2008 update and no significant changes are reported. Therefore, **naloxone HCl dihydrate manufactured and controlled as described in DMF (b) (4) is acceptable** for use in the manufacture of the drug product Suboxone® (b) (4) (buprenorphine and naloxone soluble film).
- DMF (b) (4), Naloxone HCl dihydrate manufactured by (b) (4) at their (b) (4) site, is **currently under review**. According to the DMF holder, no significant degradation of the drug substance was detected after storage at 25 °C / 60 % relative humidity (RH) for 36 months and 40 °C / 75 % RH for 6 months.

Test	Reckitt Benckiser Acceptance Criteria	Ph Eur Acceptance Criteria	USP Acceptance Criteria	Tyco/Mallinckrodt DMF Acceptance Criteria
Physical Description	White or almost white powder or (b) (4)	A white or almost white, crystalline powder, hygroscopic, freely soluble in water, soluble in alcohol, practically insoluble in toluene	-	White to off-white powder
Identification (A/C or B/C)				
A Naloxone (IR)	Positive	Positive	Positive	Matches standard
B Naloxone (TLC)	Positive	Positive	-	Matches standard
C Chloride	Positive	Positive	-	White precipitate (b) (4)
Specific optical rotation ^a	(b) (4)			
Loss on drying				
Noroxymorphone HCl and other impurities				
Chloride content ^a				
Appearance of solution	Complies with Ph Eur test	(b) (4)	-	(b) (4)
Acidity or alkalinity	Complies with Ph Eur test	Conforms	-	
Related substances	(b) (4)	(b) (4)		
	(b) (4)	(b) (4)	-	-
	(b) (4)	(b) (4)	-	-
	(b) (4)	(b) (4)	-	-
	(b) (4)	(b) (4)	-	-
Any other impurity (including impurities (b) (4))	(b) (4)	(b) (4)	-	-
Related substances (each)	-	-	-	(b) (4) x (Ph Eur) (HPLC)
Unknown related substances Total	(b) (4)	(b) (4)	(b) (4)	(b) (4) (HPLC) : (Ph Eur) (HPLC) (b) (4)
Assay ^a				
USP	98.0 to 100.5%	-	98.0 to 100.5%	98.0 to 100.5%
Ph Eur	98.0 to 102.0%	98.0 to 102.0%	-	98.0 to 102.0%
HPLC	-	-	-	98.0 to 102.0%
Identification UV (b) (4)	-	-	-	(b) (4)
(b) (4)	-	-	-	(b) (4)
Melting range ^b	-	-	-	(b) (4)

The chemical structures of the naloxone related substances are shown in Figure P-2.

Drug Product

Suboxone (b) (4) (buprenorphine/ naloxone) soluble film is a pale orange film strip, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine hydrochloride and naloxone hydrochloride dihydrate at a ratio of 4:1 (ratio as free basis), and is available in two strengths: Suboxone (b) (4) (8 mg buprenorphine/2 mg naloxone), and Suboxone (b) (4) (2 mg buprenorphine/0.5 mg naloxone).

The product is designed to deliver buprenorphine and naloxone by the sublingual (b) (4) route; it is an alternative to the currently marketed Suboxone® sublingual tablet (NDA 20-733), providing a shorter and improved oral residence time. Naloxone is included to deter diversion and misuse by injection and is not clinically available when Suboxone (b) (4) is taken as intended.

Component	Quality reference	Function	8 mg / 2 mg ^a		2 mg / 0.5 mg ^a	
			mg/strip	% (w/w)	mg/strip	% (w/w)
Buprenorphine HCl	In-House ^b	Active	8.64	17.28	2.16	5.40
Naloxone HCl Dihydrate	In-House ^b	Active	2.44	4.88	0.61	1.53
Acesulfame Potassium	NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Citric Acid, (b) (4)	USP					
(b) (4)	NF					
(b) (4)	USP					
(b) (4)	USP					
Polyethylene Oxide	NF					
(b) (4)	NF					
Polyethylene Oxide	NF					
(b) (4)	NF					
Polyethylene Oxide	NF					
Sodium Citrate (b) (4)	USP					
(b) (4) ^c	USP					
(b) (4) Lime Flavor (b) (4)	In-House	Flavorant				
FD&C Yellow No. 6	In-House	Colorant				
White Ink	In-House	Print ink	<u>Trace</u>	<u>Trace</u>	<u>Trace</u>	<u>Trace</u>
<i>Total</i>			<u>50.0</u>	<u>100.0</u>	<u>40.0</u>	<u>100.0</u>

^a "low strength" 2 mg/ 0.5 mg, dimensions 0.875" x 0.5" [mass per area: 89.1 mg/sq. inches]

"high strength" 8 mg/ 2 mg, dimensions 0.875" x 0.5" [mass per area: 114.3 mg/sq. inches]

^b In-House specifications comply with USP/Ph. Eur. and include additional controls

^c Used as a processing aid and removed during the manufacturing process

All excipients, except the flavoring agent (b) (4) Lime Flavor (b) (4) and the colorant FD&C Yellow # 6, meet compendial requirements. However, the flavoring and the colorant agents are both used in the formulation of approved Suboxone® tablets (NDA 20-733) and considered acceptable.

Suboxone® film was developed to improve and shorten the oral residence time of the currently marketed Suboxone sublingual tablets using soluble film technology. Compared to the tablets, the film formulation provides the following advantages:

- Reduced oral residence time (tablet disintegration time up to 10 minutes versus 3 minutes for the film)
- Availability in a unit dose format (pouch)
- Decreased product shipping damage (sublingual tablets are inherently more friable than regular tablets, but film strips would not suffer such damage)
- Improved child resistant packaging at the unit dose level

The flow chart, Figure P-1, summarizes the manufacturing process and in-process controls for the Suboxone (b) (4) (buprenorphine /naloxone) soluble film.



Figure P-1. Overview of the Manufacturing Process for Suboxone (b) (4)

The manufacturing process (b) (4) phases:



(b) (4)

Suboxone (b) (4) specifications are listed in Table P-2; the chemical structures of buprenorphine and naloxone known impurities are shown in Tables P-3 and P-4 respectively.

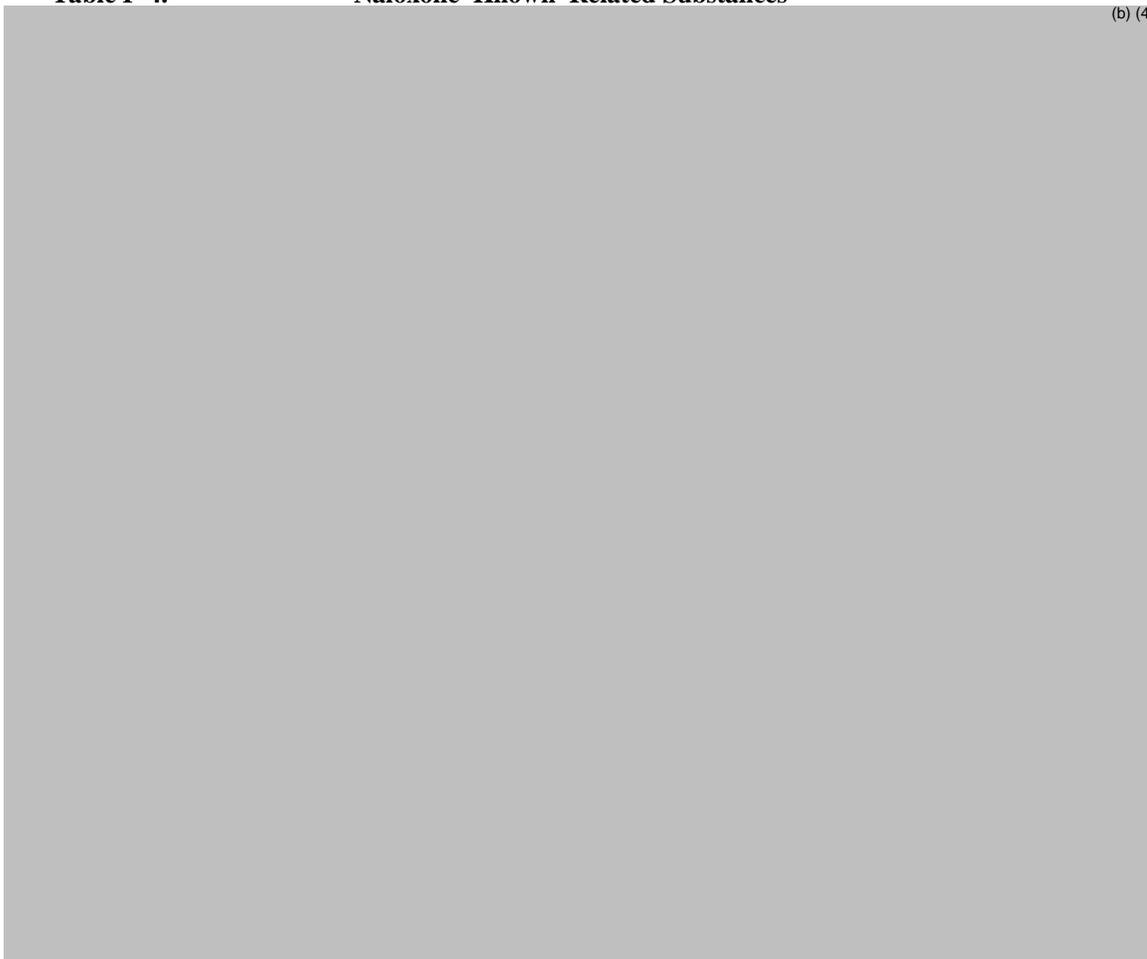
Table P-2.	Suboxone (b) (4)	Specifications	
<i>Test</i>	<i>2 mg/ 0.5 mg Acceptance Criteria</i>	<i>8 mg/ 2 mg Acceptance Criteria</i>	<i>Analytical Procedure Reference</i>
Appearance	(b) (4)	(b) (4)	Visual (SOP AN21) SAM013
Identification			
Assay: Buprenorphine			SAM013 and SAM012
Naloxone			
Buprenorphine Related Substances: (b) (4)			SAM013
Individual Unidentified Impurity Total Naloxone Related (b) (4)			SAM012 and SAM013
Individual Unidentified Impurity Total			
Dissolution: Buprenorphine Naloxone			SAM014
Moisture Content Uniformity			SAM003
Microbial Limits: ^a Total Aerobic Microbial Count Total Combined Yeast and Mold Count <i>E. coli</i> <i>Salmonella</i> Enterobacteria			SAM013; USP <905> Current USP <61> & <62> Enterobacteria by Ph.Eur.

^a = One batch to be analyzed initially, every six months and at the end of shelf life in stability studies.

^b = Results reported to 2 decimal places and (b) (4) acceptance criteria limit applied.

Table P-4. Naloxone Known Related Substances

(b) (4)



^a (b) (4) were not listed as known impurities in Suboxone Tablets (NDA 2-733).

Specification tests are claimed to be validated and fulfill their intended purpose. A justification of the specifications is provided by the applicant.

Four batches of each Suboxone ^{(b) (4)} (buprenorphine and naloxone soluble film) dosage strength are being examined as part of the stability program. The stability batches are at least ^{(b) (4)} of the proposed commercial scale with one batch of each strength at the full commercial scale; all batches have been manufactured by the commercial process and all are packed in the proposed commercial primary packaging materials. The first batch of each dosage strength was packed by a ^{(b) (4)} process, whereas the later, pivotal batches were all ^{(b) (4)} using a ^{(b) (4)} machine intended for commercial packing.

Nine (9) months stability data are provided for the first batch of each dosage strength, which lack dissolution data because a validated method was not in place. For the pivotal batches 6 month stability data at 25 °C/60 % RH, 30 °C/65 % RH, and 40 °C/75 % RH are provided.

All the facilities involved in the manufacture, testing, packaging and labeling of both drug substance and drug product have been requested for inspection. Pertinent facilities are listed in Table P-5; establishment evaluation request (EER) is attached.

Table P-5.		Establishment Information	
Responsibility	Manufacturer Name and Address	Contact Name and Telephone #	FEI or CFN
<i>Drug Substance</i> Buprenorphine Hydrochloride, Manufacturing, Packaging, Testing, and DMF Holder (DMF 12412)	Fine Chemical Plant Reckitt Benckiser Healthcare (UK) Limited Dansom Lane Hull, HU8 7DS UK	Dave Price Tel: 0044 (0)1482 582158 David.Price@ReckittBenckiser.com	CFN 9610643 FEI 3002807985

(b) (4)

Environmental Assessment

A categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(a) is claimed. According to the applicant, approval of the NDA (20-410) and marketing of Suboxone® (b) (4) (buprenorphine and naloxone soluble film) in the United States is a class of action that will not increase the use of the active moieties. Suboxone® (b) (4) (buprenorphine and naloxone soluble film) is a new dosage form that substitutes directly for Suboxone® (buprenorphine HCl and naloxone HCl sublingual tablets), an approved product (NDA 20-733). Suboxone® (b) (4) will be used for the same indication, at the same dosage levels, and for the same duration of use as Suboxone® sublingual tablets (NDA 20-733). Suboxone (b) (4) is a dosage form product line extension (new delivery system) that may be substituted directly for Suboxone® sublingual tablets (NDA 20-733). To the best knowledge of the applicant, no extraordinary circumstances exist.

IQA summary

Drug Substance

Buprenorphine hydrochloride

DMF (b) (4)

- Buprenorphine hydrochloride drug substance manufactured by Reckitt Benckiser Healthcare (UK) Ltd. according to the procedures and control given in DMF 12421 is used in the manufacture of the drug products of approved Subutex (buprenorphine) tablets (NDA 20-732) and Suboxone (buprenorphine and naloxone) sublingual tablets.
- DMF 12412 has been reviewed and deemed acceptable (2002).
- The last update to DMF 12412 is the 2008 update (Report No. RC080087) and no significant changes are reported.
- Therefore, **buprenorphine HCl drug substance manufactured and controlled as described in DMF 12412 is acceptable** for use in the manufacture of the drug product Suboxone® (b) (4) (buprenorphine and naloxone soluble film).

Naloxone hydrochloride dihydrate

(b) (4)

Drug Product

- The drug product Suboxone (b) (4) is an alternative to the currently marketed Suboxone® sublingual tablet (NDA 20-733).
- The description and composition of the drug product is adequately provided.
- Pharmaceutical development is described, and the rationale for a soluble film dosage with short disintegration time (desired attribute of the drug product) is provided.
- Manufacturing facilities and their responsibilities are given. The manufacturing process is conventional.
- Adequacy of in-process control is a review issue.
- Executed batches provided.
- Besides the flavoring (b) (4) Lime Flavor (b) (4), the colorant FD&C Yellow # 6, and White ink, all other excipients meet compendial requirements.
- (b) (4) Lime Flavor (b) (4) and FD&C Yellow # 6 are non compendial excipients are used in the formulation of approved Suboxone® sublingual tablet (NDA 20-733). The white ink is an edible grade supplied by (b) (4); all ink components are compendial, and the level of the ink in the film strip is a trace amount.

- The drug product specifications, although similar to those for Suboxone® sublingual tablet (NDA 20-733), differ –as expected– in the acceptance criteria for identification, dissolution and additional requirements for four additional known impurities not observed in the tablet counterpart.
- The acceptability of the acceptance criteria for these four previously mentioned known impurities (b) (4) is a review issue.
- Specification tests are claimed to be validated and fulfill their intended purpose. A justification of the specifications is provided by the applicant.
- The proposed test methods are well known and widely used by the pharmaceutical industry. Consequently, revalidation of analytical methods by Agency laboratories is not recommended.
- Soloxone film strips are packed individually into pouches. The acceptability of the material (pouch component) in contact with the film product should be evaluated.
- Four batches of each Suboxone (b) (4) (buprenorphine and naloxone soluble film) dosage strength are being examined as part of the stability program. The stability batches are at least (b) (4) of the proposed commercial scale with one batch of each strength at the full commercial scale; all batches have been manufactured by the commercial process and all are packed in the proposed commercial primary packaging materials.
- At least six (6) most of stability data is provided per batch.
- Requested expiration date is (b) (4), stored a room temperature. Acceptability of the proposed expiry dating is a review issue.
- A categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(a) is claimed, and the criteria is met.

Overall evaluation: There are no CMC standing issues that preclude the filing of NDA 22-410. This NDA relies partially on the information previously submitted to their other two NDAs, Subutex (Buprenorphine) Tablets 2 mg and 8 mg, (NDA 20-732) and Suboxone® (Buprenorphine and Naloxone) sublingual tablet (NDA 20-733). The main goal of the proposed product Suboxone (b) (4) which is to provide an alternative to Suboxone Tablets with a shorter oral residence time by the development of a soluble film dosage product, is accomplished by the applicant. Although there are not standing issues, minor requests to the applicant as the review progresses may be send to the applicant.

	Xavier Ysern, PhD	Review Chemist	ONDQA/ DPA I/ Branch II
Init.	Ali Al-Hakim, PhD	Branch Chief	ONDQA/ DPA I/ Branch II

Attached:

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application : NDA 22410/000 Sponsor: RECKITT BENCKISER
 Org Code : 170 10710 MIDLOTHIAN TPKE STE 430
 Priority : RICHMOND, VA 23235

Stamp Date : 21-OCT-2008 Brand Name : BUPRENORPHIN/NALOXONE 2MG/8MG
 PDUFA Date : 21-AUG-2009 FILM STRIP
 Action Goal : Estab. Name:

District Goal: 22-JUN-2009 Generic Name: BUPRENORPHON/NALONE 2MG/8MG
 Dosage Form: FILM STRIPS
 Strength : (TROCHE)
 2MG/5MG AND 2MG/0.5MG

FDA Contacts: X. YSERN Review Chemist 301-796-2410
 D. CHRISTODOULOU Team Leader 301-796-1342

--Overall Recommendation: -----

Establishment : CFN : (b) (4) FEI : (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : NEC OAI Status: NONE
 Last Milestone: SUBMITTED TO OC
 Milestone Date: 05-DEC-08
 :
 :

Establishment : CFN : (b) (4) FEI : (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : NEC OAI Status: NONE
 Last Milestone: SUBMITTED TO OC
 Milestone Date: 05-DEC-08
 :
 :

Establishment : CFN : (b) (4) FEI : (b) (4)
 (b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08
:
:

Establishment : CFN : (b) (4) FEI : (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : NEC OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08
:
:

Establishment : CFN : (b) (4) FEI : (b) (4)
(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08
:
:

Establishment : CFN : (b) (4) FEI :

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Profile : NEC OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08
:
:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment : CFN : 9610643 FEI : 3002807985
 RECKITT BENCKISER PLC
 CHAPMAN STREET & DANSON LANE
 HULL, EAST YORKSHIRE, UK HU8 7DS
DMF No: 12412 AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date: 05-DEC-08
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/s/

Xavier Ysern
12/12/2008 02:25:42 PM
CHEMIST

Ali Al-Hakim
12/12/2008 04:31:28 PM
CHEMIST