

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205637Orig1s000**

**SUMMARY REVIEW**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
 Division of Anesthesia, Analgesia, and Addiction Products  
 10903 New Hampshire Ave.  
 Silver Spring, MD 20993-0002

**Summary Review for Regulatory Action**

<b>Date</b>	June 6, 2014
<b>From</b>	Rigoberto Roca, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/Supplement No.</b>	205637/S-000
<b>Applicant Name</b>	BioDelivery Sciences International, Inc.
<b>Date of Submission</b>	August 7, 2013
<b>PDUFA Goal Date</b>	June 7, 2014
<b>Proprietary Name / Established (USAN) Name</b>	Bunavail / (buprenorphine and naloxone) buccal film
<b>Dosage Forms / Strength</b>	<ul style="list-style-type: none"> <li>• 2.1/0.35 mg buprenorphine/naloxone buccal film</li> <li>• 4.2/0.7 mg buprenorphine/naloxone buccal film</li> <li>• 6.3/1.04 mg buprenorphine/naloxone buccal film</li> </ul>
<b>Proposed Indication</b>	Maintenance treatment of opioid addiction
<b>Action</b>	Approval

<b>Material Reviewed/Consulted:</b> OND Action Package, including	
Medical Officer Review	Pamela Horn, MD
CDTL Review	Celia Winchell, MD
Statistical Review	Sutan Wu PhD / Yi Tsong, PhD
Pharmacology Toxicology Review	Gary Bond, PhD / Adam Wasserman, PhD
ONDQA Review	Arthur Shaw, PhD / Prasad Peri, PhD
Product Quality Microbiology	John Metcalfe, PhD / Stephen Langille, PhD
Clinical Pharmacology Review	Wei Qiu, PhD / Yun Xu, PhD
Pharmacometrics Review	Kareen Riviere, PhD / Tapash Ghosh, PhD
Project Management Staff	Matthew Sullivan, MS
Controlled Substance Staff	Silvia Calderon, PhD / Michael Klein, PhD
OMP/DMPP and OPDP	Nathan Caulk, MS, BSN, RN / L. Shenee' Toombs, PharmD / Barbara Fuller, RN, MSN / LaShawn Griffiths, MSHS-PH, BSN, RN
OSI/DBGLPC	Arindam Dasgupta, PhD / Chase Bourke, PhD
OSE/DMEPA	Vicky Borders-Hemphill, PharmD / Irene Chan, PharmD

CDTL = Cross-Discipline Team Leader  
 DBGLPC = Division of Bioequivalence and Good Laboratory Practice Compliance  
 DGMPA = Division of Good Manufacturing Practice Assessment  
 DMEPA = Division of Medication Error Prevention and Analysis  
 DMPP = Division of Medical Policy Programs  
 DRISK = Division of Risk Management

OMP = Office of Medical Policy  
 OND = Office of New Drugs  
 ONDQA = Office of New Drug Quality Assessment  
 OPDP = Office of Professional Drug Promotion  
 OSE = Office of Surveillance and Epidemiology  
 OSI = Office of Scientific

## 1. Introduction

BioDelivery Sciences International, Inc. (the Applicant), has submitted a 505(b)(2) new drug application (NDA) for buprenorphine/naloxone, formulated as a film that is intended for placement adjacent to the buccal mucosa. The reference product is Suboxone (NDA 20733), a buprenorphine/naloxone tablet intended for sublingual administration. The proposed indication is for maintenance treatment of opioid addiction. The proposed proprietary name is “Bunavail,” which has been found to be acceptable.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

## 2. Background

### Buprenorphine

Buprenorphine is a partial agonist at the  $\mu$ -opiate receptor. Buprenorphine was initially approved in 1981 as a parenteral formulation for the treatment of pain (Buprenex, NDA 18401). Since 1981, there have been five NDAs containing buprenorphine approved:

- Three sublingual tablet formulations intended for treatment of opioid dependence
  - Subutex (buprenorphine), NDA 20732
  - Suboxone (buprenorphine/naloxone), NDA 20733
  - Zubsolv (buprenorphine/naloxone), NDA 204242
- Sublingual film formulation intended for treatment of opioid dependence
  - Suboxone (buprenorphine/naloxone) film, NDA 22410
- Extended-release transdermal film formulation intended for the treatment pain
  - Butrans (buprenorphine), NDA 21306

As noted in Dr. Horn’s and Dr. Winchell’s reviews, buprenorphine was developed as a treatment for opioid dependence because of its pharmacological properties. Buprenorphine’s activity at the  $\mu$ -receptor was expected to relieve the patient’s urge to use illicit opioids, and its long duration of action would allow a patient to achieve a steady state without the highs and lows associated with illicit opioids. Further, its partial agonist property was expected to result in a “ceiling” effect at moderate doses with respect to its euphorogenic effects. Lastly, at sufficiently high doses, buprenorphine blocks full agonists from achieving their full effects, which, in buprenorphine-maintained patients, would result in decreased use of these substances.

### Naloxone

Naloxone is a  $\mu$ -receptor antagonist, which, when used parenterally, produces opioid withdrawal signs and symptoms in subjects who are dependent on full opioid agonists. The incorporation of naloxone into Bunavail’s formulation is not for the purposes of treating the opioid addiction, but rather, to provide an additional element of deterrence for intravenous misuse. As noted in Dr. Horn’s and Dr. Winchell’s reviews, the naloxone is expected to be clinically inactive when the product is used as intended.

### Pre-submission Regulatory History

The major interactions between the Division and the Applicant prior to the submission of the NDA are well-summarized in Dr. Horn's and Dr. Winchell's reviews. Significant recommendations conveyed to the Applicant included the following:

- No clinical efficacy or safety data regarding systemic exposure would be required if the systemic buprenorphine exposure was bioequivalent to the reference product.
- Patients would need to undergo an oral examination to assess for any local toxicity.
- Increased bioavailability of the Applicant's product would require that the naloxone content be reduced to an amount that, when Bunavail is used as intended, would result in plasma levels that are not higher than the reference product.
- If the reduction in the amount of naloxone would result in a different buprenorphine/naloxone ratio than what is contained in the reference product, the Applicant would need to demonstrate that the amount of naloxone in the final formulation was sufficient to produce an aversive effect under conditions of misuse.
- The Applicant would need to submit additional data to support an indication of (b) (4) (u) (4) of opioid dependence, because the reference product is not indicated for (b) (4) (u) (4).
- Extraction studies would not be required for the NDA submission if the Applicant is not seeking any abuse-deterrent language to be included in the package insert.

## 3. Chemistry, Manufacturing, and Controls (CMC)

### General Product Considerations

#### Drug Substances

There are two drug substances, buprenorphine hydrochloride and naloxone hydrochloride. The following is reproduced from Dr. Shaw's review regarding the buprenorphine:

Complete CMC information is provided in DMF (b) (4), which was reviewed and found acceptable in a review dated February 18, 2014. It is a white solid that is slightly soluble in water. Since the drug substance is (b) (4) to manufacture the drug product the solid state form is not relevant to the drug product characteristics. The DMF holder adequately controls the impurities. The applicant accepts the drug substance based on the supplier's COA and their own ID test by IR and has the drug substance fully tested by a contract laboratory.

The following is reproduced from Dr. Shaw's review regarding the naloxone:

Complete CMC information is provided in DMF (b) (4), which was reviewed and found acceptable in a review dated November 22, 2013. It is a white solid that is soluble in water. Since the drug substance is (b) (4) to manufacture the drug product the solid state form is not relevant to the drug product characteristics. The DMF holder adequately controls the impurities. The applicant accepts the drug substance based on the supplier's COA and their own ID test by IR and has the drug substance fully tested by a contract laboratory.

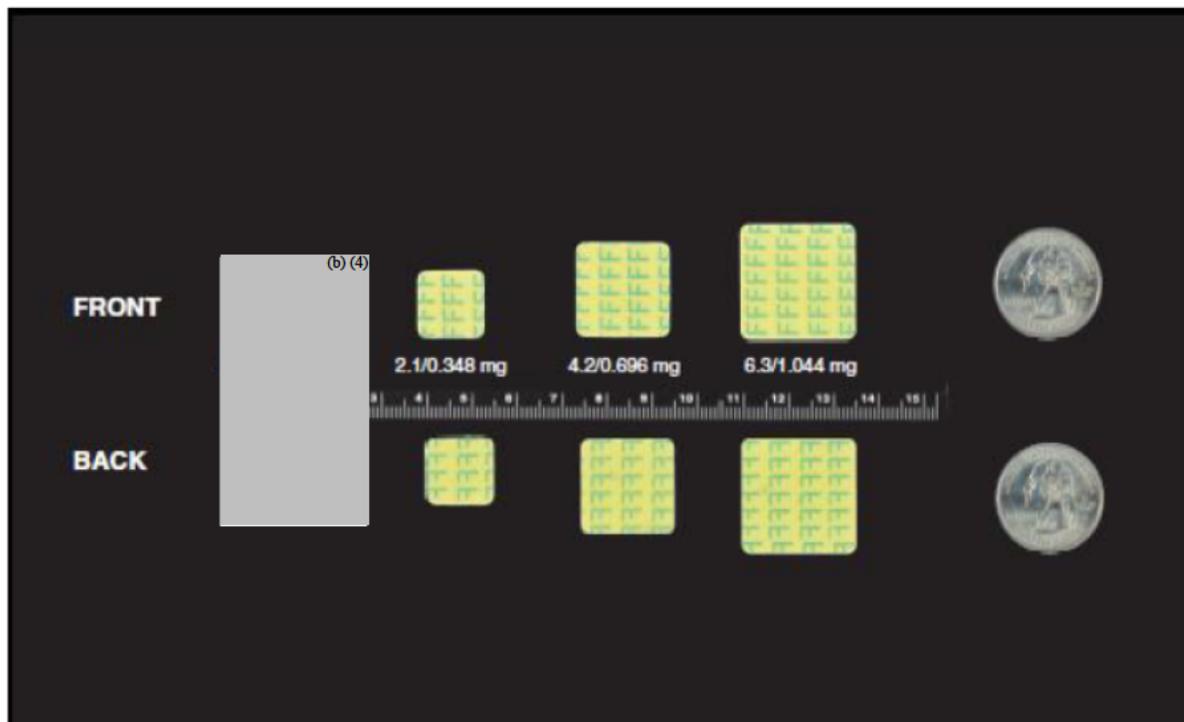
### Drug Product

The drug product consists of a polymeric film containing two layers, each with one of the two drug substances. One layer is considered the “mucoadhesive layer” and contains the buprenorphine. The other layer is considered the “backing layer” and contains the naloxone. The Applicant has used the term BioErodable MucoAdhesive, or BEMA, to refer to their formulation platform.

As noted in Dr. Shaw’s review, the two layers are (b) (4) but cannot be distinguished from each other nor peeled apart in the finished product. The film is yellow in color, and the different strengths have (b) (4) compositions but are of different sizes. The strength of the dose is printed on the film in such a manner so that the patient is able to determine which side is supposed to be applied against the buccal mucosa. When used as intended, the buprenorphine is absorbed as the film dissolves, and the naloxone is swallowed.

The following figure, reproduced from the Applicant’s submission, illustrates the color and relative sizes of the different dosage strengths (to each other, as well as to a U.S. quarter dollar coin).

**Figure 1**



It is not possible to distinguish the front side of the film from the back side of the film in the photograph; however, a non-buprenorphine-containing sample was provided by the Applicant to the review team and it was confirmed that the printing was clearly legible and that proper orientation of the film for proper placement would not be a concern.

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### Specific Issues Identified in the Course of the Review

#### *Assessment of Film Adhesion to Buccal Mucosa*

The Applicant did not conduct any validated in vitro test to assess the film's ability to adhere to the buccal mucosa. Therefore, the review team evaluated the clinical data for evidence of any problems with respect to adhesion of the film when used as directed. The Applicant submitted a tabulation of medical errors from Study BNX-201, an open-label safety study conducted by the Applicant to assess for local tolerability and toxicity. In that study, issues relating to poor adhesion were reported by 6 (2%) of the 249 participants.

#### *Inspection of Manufacturing Facilities*

As noted in Dr. Shaw's review, the manufacturing facilities were deemed acceptable.

#### *Stability Data*

The data in the NDA submission support a 12-month expiry date. The Applicant had requested an expiration date period of (b) (4), based on extrapolation of the 12-month data. However, Dr. Shaw noted in his review that such extrapolation was not possible in this case because an unidentified impurity was noted to be increased at both intermediate and accelerated storage conditions.

#### *Extraction Studies*

As noted in Dr. Shaw's review, and summarized in Dr. Winchell's review, the Applicant conducted several extraction studies to determine whether there could be differential extraction of the buprenorphine and/or naloxone. The following synopsis is reproduced from Dr. Winchell's review:

The studies show that buprenorphine can be selectively extracted in (b) (4) from both Bunavail films and Suboxone tablets, leaving the naloxone behind and yielding a solution of buprenorphine dissolved in (b) (4). However, unlike the tablet, which disintegrates into the solution although the naloxone does not dissolve, the film remains intact and could be removed, taking the naloxone with it. It is noted, however, that there are also methods of separating the naloxone from buprenorphine in the reference tablet product.

These results were not deemed to be an approvability issue and are further discussed below, in Section 11 of this review.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by the product quality review team that there are no outstanding or unresolved CMC issues that would preclude approval of this application.

## **4. Nonclinical Pharmacology/Toxicology**

#### General Considerations

A full nonclinical pharmacology/toxicology program to assess the overall systemic toxicity was not required or submitted for this application. The Applicant, however, did conduct a 28-study in the dog model with a BEMA disc to assess local toxicity of their formulation. The disc that was studied did not contain any naloxone, and it only contained approximately one quarter of the

amount of buprenorphine that was to be incorporated into the to-be-marketed product. Subsequently, the study was primarily informative about the potential for local toxicity of the excipients present in the formulation.

The local toxicity noted was limited to minimal to slight inflammation of the oral mucosa. In addition, the non-clinical assessment and conclusions indicated no concerns noted with regard to safety issues due to impurities, degradants, or excipients.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Bond and Wasserman that there are no pharmacology/toxicology issues that would preclude approval of this application.

## **5. Clinical Pharmacology/Biopharmaceutics**

The details of the clinical pharmacology assessments submitted in the NDA are well-detailed in the review by Dr. Qui. The major findings are summarized below, adapted from Dr. Qui's review:

1. Bunavail buccal film 1 x 4.2/0.7 mg exhibited equivalent systemic exposure ( $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ ) to buprenorphine in comparison to the listed drug, Suboxone sublingual tablet 1 x 8/2 mg.
2. Bunavail buccal film 1 x 4.2/0.7 mg had 27% lower naloxone  $C_{max}$ , 33% lower naloxone  $AUC_{last}$ , and 34% lower naloxone  $AUC_{inf}$  values in comparison to Suboxone sublingual tablet 1 x 8/2 mg.
3. Dose-proportionality was not demonstrated for buprenorphine  $C_{max}$  and AUC values over the range of 0.875 mg to 5.25 mg following the administration of Bunavail buccal films of 1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 0.875 to 5.25 mg. There was a dose proportional increase in buprenorphine  $C_{max}$  and AUC values as dose increased from 4.2 to 6.3 mg following the administration of Bunavail buccal films of 1 x 4.2/0.7 mg and 1 x 6.3/1.04 mg.
4. Dose-proportionality was not demonstrated for naloxone  $C_{max}$  and AUC values over the range of 0.15 mg and 0.9 mg following the administration of Bunavail buccal films of 1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 0.15 to 0.9 mg. There was a dose proportional increase in naloxone  $C_{max}$  and AUC values as dose increased from 0.7 to 1.04 mg following the administration of Bunavail buccal films of 1 x 4.2/0.7 mg and 1 x 6.3/1.04 mg.
5. Co-administration of low or high pH liquids lowered the  $C_{max}$  and AUC values of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  values for

buprenorphine being reduced by 59%, 52%, and 49%, respectively, compared to when no liquids were co-administered. The  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  values for naloxone were reduced by 76%, 74%, and 72%, respectively. The high pH fluid intake also reduced the systemic exposures of buprenorphine and naloxone. Buprenorphine  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  were reduced by 26%, 24%, and 24%, respectively, and naloxone  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  were reduced by 41%, 42%, and 40%, respectively. Caution language will be added to the label stating not to take the product with drink or food.

6. Biowaiver for Bunavail buccal film 2.1/0.348 mg has been granted based on dissolution data. However, the biowaiver request for Bunavail buccal film (b) (4) mg is not granted (b) (4).

7.



Information regarding the pharmacokinetic characteristics of the buprenorphine and naloxone was derived from the information known about the reference drug, Suboxone sublingual tablet. The following paragraphs are reproduced from Dr. Qui's review:

Plasma levels of buprenorphine increased with sublingual doses (in the range of 4 to 16 mg) but not in a directly dose-proportional manner. Naloxone did not affect the pharmacokinetics of buprenorphine. There was a trend toward an increase in naloxone concentrations with increase in dose. At the three naloxone doses of 1, 2, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects.

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Elimination half-life of buprenorphine ranges from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours.

### *Hepatic Impairment*

As noted in Dr. Winchell's review, recently-reviewed data of another buprenorphine/naloxone product has demonstrated that hepatic impairment differentially affects the pharmacokinetics of buprenorphine and naloxone. In subjects with mild hepatic impairment, the changes in mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone are not clinically significant and no dosing adjustment is needed.

However, in subjects with moderate or severe hepatic impairment, mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone are increased, more so in naloxone than in buprenorphine. More significantly, the increase in naloxone exposure is 10-fold or greater in patients with severe hepatic impairment, which has potential implications for both safety and efficacy. Subsequently, buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. This information will be incorporated into the label.

### *Renal Impairment*

Renal impairment does not affect buprenorphine pharmacokinetics; the effects on naloxone pharmacokinetics are unknown.

### *Biowaiver Request*

In order to be able to rely on the Agency's prior findings of the referenced drug, the Applicant conducted a bioequivalence study comparing the Bunavail 4.2/0.7 mg (buprenorphine/naloxone) strength to the 8/2 mg strength Suboxone sublingual tablet. In addition, they conducted a study to demonstrate dose proportionality between the 4.2/0.7 mg strength and the 6.3/1.04 mg strength Bunavail films. The Applicant requested a waiver from the requirement to conduct bioavailability/bioequivalence (BA/BE) studies for the two lowest Bunavail dosage strengths. As noted in Dr. Riviere's review, a waiver for conducting in vivo studies could be considered if the following conditions are met:

- The lower strength(s) and higher strength product have the same dosage form;
- There are BA/BE data for the highest strength;
- The lower strength(s) product is proportionally similar in its active and inactive ingredients to the highest strength product; and
- Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.

The results of the data from the studies are well described in Dr. Riviere's review and summarized in Dr. Winchell's review. The final conclusion of the biopharmaceutics review team was that a biowaiver could be granted for the 2.1/0.35 mg dosage strength, but not the (b) (4) mg dosage strength. Based on the data submitted in the NDA, the recommendation,

from a biopharmaceutics standpoint, was that the data supported the approval of only the top three dosage strengths (i.e., the 2.1/0.35 mg, 4.2/0.7 mg and 6.3/1.04 mg strengths).

The assessment by the biopharmaceutics team was conveyed to the Application in a Discipline Review letter on May 9, 2014. After additional discussions with the division, the Applicant requested to withdraw the lowest dosage strength from the application on May 30, 2104, <sup>(b) (4)</sup>

#### Assessment of Cardiac Conduction Effects

In interactions with the Applicant during the course of drug development, the Division noted that a study in another buprenorphine product had demonstrated a signal for QT prolongation that had met the threshold for regulatory significance. The Applicant was informed that, in the event that a definitive assessment of buprenorphine's potential for QT prolongation was not available for incorporation by reference at the time of their NDA submission, a study would be required. However, the data from such a study could be submitted as a post-marketing commitment.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Qiu and Xu that there are no clinical pharmacology issues that would preclude approval of this application.

## **6. Clinical Microbiology**

Bunavail is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

## **7. Clinical/Statistical – Efficacy**

As noted by Dr. Horn and Dr. Winchell in their respective reviews, the Applicant was not required to submit additional data demonstrating the clinical efficacy of buprenorphine. However, because the buprenorphine/naloxone ratio in Bunavail is approximately 6:1, the Applicant needed to submit data demonstrating that this amount naloxone would perform as intended, i.e., cause adverse effect if the product was crushed and injected intravenously.

The Applicant submitted the results of Study LCR-04-01-01, a double-blind, placebo-controlled, four-treatment, four-period crossover study. The study enrolled subjects with moderate-to-severe non-cancer pain requiring at least 100 mg of oral morphine daily for at least 3 months.

The following description of the study is reproduced from Dr. Winchell's review:

...[subjects] were to continue to receive opioid at the same dose on the same schedule and receive four test articles administered intravenously (buprenorphine 0.75 mg; buprenorphine 0.75 mg + naloxone 0.1 mg; buprenorphine 0.75 mg + naloxone 0.2 mg; placebo) intended to induce withdrawal symptoms consecutively in random order, with three days between test articles to minimize any carryover effects. Withdrawal in response to the test articles was to be measured using the Clinical Opiate Withdrawal

Scale, physiologic, and subject rated-measurements. The primary analysis comparing test articles was to be performed on the COWS scores.

To be eligible, subjects also had to display signs and symptoms of withdrawal (as evidenced by A COWS score of  $\geq 5$ ) in response to a challenge of naloxone, administered in 0.05 mg increments every five minutes until the target COWS was reached or a total of 0.2 mg had been administered.

The results of the study were summarized by Dr. Horn as follows:

The results in change from baseline in COWS scores support the effectiveness of buprenorphine and buprenorphine with naloxone at the two doses studied in causing clinically significant withdrawal in a substantial proportion of subjects. Naloxone appeared to worsen withdrawal symptoms in a dose-dependent fashion above what was observed with buprenorphine alone. The results on the COWS were supported by the trends observed in the physiological measures, even though many of the physiological measures were taken after rescue medication administration.

The COWS results are well-supported by the pattern of rescue medication use, which was administered based on COWS scores above 13 and indicated that subjects were experiencing withdrawal in a pattern consistent with the overall COWS data.

The subjects were on clinically relevant opioid maintenance doses in this study and the results can be reasonably be generalized to those with a physical dependence to full opioid agonists who would attempt to inject this product. Buprenorphine and naloxone in a ratio of 7.5 to 1 at a naloxone dose of 0.1 mg resulted in more withdrawal than buprenorphine alone, indicating that this ratio of buprenorphine to naloxone and this amount of naloxone is sufficient to increase the aversive effects of the product when injected. The amount of naloxone in the lowest dose of the product is (b) (4), which is more than 0.1 mg and it is combined with (b) (4) mg buprenorphine in a 6:1 ratio, which is a lower ratio than the 7.5:1 ratio in the study.

Therefore, the study results support including naloxone at the dose and ratio contained in the product.

It is noted that, as of the date of this memo, the Applicant is no longer seeking approval of the lowest dose strength presentation and has withdrawn it from the NDA submission.

#### Outstanding or Unresolved Issues

I concur with the overall conclusion reached by Drs. Horn and Winchell that there are no efficacy concerns that would preclude approval of this application.

## **8. Safety**

The Applicant was not required to submit additional safety data regarding the systemic exposure to buprenorphine, provided that their product did not exceed the exposure levels obtained by the reference product. However, because this was a novel dosage form and route of administration, the Applicant was required to submit data from a study evaluating the local tolerability and toxicity.

Study BNX-201 was a 12-week open label study in patients who had been maintained on Suboxone tablets or films at doses between 8 mg and 32 mg per day, for at least 30 days. The patients were to have no baseline abnormalities of the buccal mucosa that would preclude absorption. Examinations of the oral cavity were to be performed by physician investigators on Days 7, 14, 28, 56, and 84. The examiner was trained by a dentist in order to ensure that the examiner knew what to look for, as well as to maintain a level of consistency in the study.

The results of the study are well detailed in Dr. Horn's and Dr. Winchell's respective review, and are only briefly summarized here:

- A total of 249 patients participated in the study
- The mean age was 39 years (range: 20 to 62)
- The subject population was predominantly male (66%)
- Mean dose of Suboxone at study entry was 16 mg per day (range: 8 to 32 mg per day)

The dispositions of subjects are summarized in the table below, adapted from Table 14.1.1 in the Applicant's Clinical Study Report. The safety population was defined as consisting of all subjects who took at least one dose of study drug.

Subject Disposition, Study BNX-201

	N (%)	
Safety Population	249 (100)	
Completed study	197 (79)	
Discontinued	52 (21)	
Reason for Discontinuation		
Adverse event	6 (2)	
Right hallux osteomyelitis		1 (0.4)
Suicidal ideation		1 (0.4)
Headache		1 (0.4)
Positive urine toxicology screen		2 (0.8)
Oral ulcer		1 (0.4)
Subject experiencing withdrawal symptoms	5 (2)	
Withdrew consent	16 (6)	
Personal problems, transportation, or job issues		8 (3)
Ineffective for tooth pain		1 (0.4)
Irritability and lack of concentration		1 (0.4)
Wanted to go back on Suboxone		1 (0.4)
Didn't want to be in the study anymore		1 (0.4)
Relapsed to opioid use		2 (0.8)
Didn't want to disclose information about losing a dose to staff		1 (0.4)
Difficulty applying film due to orthodontic appliances		1 (0.4)
Lost to follow-up	7 (3)	
Study terminated by sponsor	0	
Other	18 (7)	
Noncompliant		10 (4)
Uncontrolled diabetes		1 (0.4)
Pregnancy		1 (0.4)
Moved out of the area		1 (0.4)

Disallowed medications		2 (0.8)
Elevated baseline creatinine		1 (0.4)
Unknown		2 (0.8)

Dr. Horn was able to identify the underlying reasons for the two largest categories, “withdrew consent” and “other,” and was able to establish that, for the vast majority, these did not appear to be attributable to any treatment-related adverse event.

#### *Deaths*

There were no deaths identified in the safety database.

#### *Non-fatal Serious Adverse Events*

There were two serious adverse events reported in the Study: a subject with osteomyelitis of the right hallux, and a subject with suicidal ideation. The review team did not feel that either of these events was likely to be due to the formulation, as both of them had been on Suboxone tablets at the beginning of the study, and a change in the formulation would not be expected to have resulted in these adverse events.

#### *Early Discontinuations*

Adverse events that resulted in early discontinuations were the two serious adverse events noted above, as well as the events noted in the table summarizing the subjects’ dispositions. It is worth noting that the subject that discontinued due to an oral ulcer did not have any buprenorphine in their urine, indicating that the subject was not taking the product.

#### *Common Adverse Events*

The most commonly reported adverse event were the signs and symptoms associated with drug withdrawal, reported in approximately 35% of the subjects. This was consistent the results of the clinical pharmacology study which indicated that the dose conversion paradigm utilized in this study resulted in subjects being assigned to too low a dose of Bunavail, an assessment corroborated by the proportion of subjects who needed to have their doses increased during the course of the study.

There were no safety findings of concern related to vital signs, laboratory assessments, or electrocardiographic evaluations.

#### *Assessment for local toxicity*

Of the 249 subjects enrolled in the study, 3 subjects had mild mucosal redness, and 2 subjects were observed to have swelling or raised lesions. In all cases, the findings resolved without study drug treatment discontinuation.

As noted above, one subject was reported to have discontinued secondary to an oral ulcer, but he was found to not have been taking the study drug treatment.

The review team’s conclusion was that the study did not identify any local toxicity concerns for the proposed formulation.

*Risk Evaluation and Mitigation Strategy (REMS)*

All ANDA-holders of buprenorphine-containing transmucosal products approved for the treatment of opioid dependence are obliged to participate in the shared system REMS known as “BTOD” – an acronym for “buprenorphine-containing transmucosal products for opioid dependence.” NDA holders are not subject to this requirement; however, in order to reduce the burden on the healthcare systems, NDA holders are being asked to also participate in this shared system. The Applicant has agreed to do so.

The goals of the REMS are to:

1. Mitigate the risks of accidental overdose, misuse, and abuse
2. Inform patients of the serious risks associated with buprenorphine-containing products

The elements of the REMS are:

1. Medication Guide
2. Elements to Assure Safe Use
  - Safe use Conditions
  - Monitoring
3. Implementation System
4. Timetable for Submission of Assessments

Additional materials in the REMS include:

For Prescribers

1. Dear Prescriber Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers
3. Appropriate Use Checklist

For Pharmacists

1. Dear Pharmacist Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

For Patients

1. Medication Guide

Dr. Winchell noted in her review that the REMS material that will be approved for Bunavail will not include the information about the different pharmacokinetic profile in patients with moderate to severe hepatic impairment, but it will be included in the labeling. The reason for this omission is primarily logistical and administrative. It would not be optimal to have the newest member of the shared system have information in their REMS that is different from the rest of the group, and since the group is going to have to incorporate Bunavail’s product information into its material, that will offer an opportunity to modify the materials with respect to the hepatic impairment information.

From a practical standpoint, Bunavail will not be marketed without this information in its REMS because it will only be marketed with the REMS from the BTOD group, which as noted above, will be including this information at the time it adds Bunavail’s product information.

### Outstanding or Unresolved Issues

I concur with Drs. Horn and Winchell that the safety profile of Bunavail has been adequately established and that there are no safety concerns that would preclude approval of this application.

## **9. Advisory Committee Meeting**

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

## **10. Pediatrics**

The Applicant requested a waiver of the requirements for the studies stipulated by the Pediatric Research Act (PREA) of 2003. The rationale for the neonate age group (0 to 5 weeks of age) was based on safety concerns: although buprenorphine could theoretically be used to treat neonatal abstinence syndrome, the product contains naloxone, which would not have a purpose in this clinical scenario, and would have potential safety concerns.

With respect to the older age groups (older than 5 weeks and up to 16 years of age), the Applicant indicated that such studies would be impossible or highly impracticable, due to the low prevalence of opioid abuse and dependence in this patient population.

The Division concurred with the Applicant's rationale, and presented the information to the Pediatric Review Committee (PeRC), which agreed that a full waiver should be granted.

## **11. Other Relevant Regulatory Issues**

### Reference Drug Identified for 505(b)(2) Purposes

The Applicant has referenced the Suboxone application (NDA 20733) for purposes of relying on the Agency's previous finding of safety and efficacy of a buprenorphine/naloxone product. The manufacture of Suboxone, Reckitt Benckiser, has withdrawn the product from U.S. marketing. The Agency has determined that the Suboxone tablets were not withdrawn from sale for reasons of safety or effectiveness. The reference application is now listed in the Discontinued section of the Orange Book.

### OSI / Division of Bioequivalence and GLP Compliance Audit

Study BNX-110 constituted the pivotal bioequivalence study. The clinical portion of the study was audited between December 4<sup>th</sup> and 9<sup>th</sup> 2014, and the analytical portion of the study was audited between [REDACTED] (b) (4)

A Form 483 was issued to the clinical site, and a response was received by OSI on April 23, 2014. It was deemed acceptable. No Form 483 was issued for the analytical portion of the study.

The final conclusion and recommendation by the Division of Bioequivalence and GLP Compliance was that the data from Study BNX-110 were acceptable.

Assessment by the Controlled Substances Staff

The Controlled Substances Staff were consulted to review the NDA submission from a controlled substance/abuse potential perspective. Dr. Calderon's review noted the results of the extraction studies and noted that, although buprenorphine could be selectively extracted from the film, the language proposed by the Applicant in Section 5.8 of the label was still applicable. Specifically, the wording is:

Section 5.8 – Precipitation of Opioid Withdrawal Signs and Symptoms

*Because it contains naloxone, BUNAVAIL buccal film is highly likely to produce (b) (4) withdrawal signs and symptoms if misused parenterally by Individuals dependent on full opioid agonists such as heroin, morphine and methadone. Because of the partial agonist properties of buprenorphine, BUNAVAIL buccal film may precipitate withdrawal signs and symptoms in such persons if administered buccally before the agonist effects of the opioid have subsided.*

Dr. Calderon noted in her review:

It is likely that the naloxone extracted from the film in combination with buprenorphine using common extraction solvents such as (b) (4) will precipitate withdrawal signs and symptoms if the film were abused by the parenteral route by individuals dependent on full opioid agonist.

Dr. Calderon's review indicated that she had no specific recommendations as this time. The review team concurred with the Controlled Substance Staff assessment and did not consider this finding an approvability issue. The product's labeling regarding the potential for abuse, the NDA holder's participation in the BTOD shared system REMS, and the data supporting its safety and effectiveness when used as directed in the label makes its risk comparable to other currently approved and marketed products.

Financial Disclosure

The Applicant certified that there was no financial arrangement with the study investigators whereby the value of compensation to the investigators could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that no listed investigator was the recipient of significant payments of sorts as defined in 21 CFR 54.2 (f). The Applicant also indicated that the clinical investigators were required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant, as defined in 21 CFR 54.2(b).

Legal and Regulatory Constraints

Buprenorphine is a Schedule III Controlled Substance, and subject to the requirements and regulations stipulated by the Controlled Substances Act. However, there are additional regulations when it used as agonist therapy in the treatment of opioid addiction, which are different than those imposed on methadone. Dr. Winchell summarized these distinctions in her review, and that summary is reproduced below:

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The

current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine.

### Outstanding or Unresolved Issues

There are no outstanding or unresolved relevant regulatory issues.

## 12. Labeling

Consultations were obtained from the Controlled Substances Staff, Office of Scientific Investigations (OSI), the Office of Professional Drug Promotion, the Division of Risk Management, and the Division of Medication Error Prevention and Analysis. Their recommendations were reviewed and incorporated in the appropriate places in the label.

The key differences between the label proposed by the Applicant and the label that was deemed appropriate by the review team are summarized in Dr. Winchell's review, and reproduced below.

- References to the lowest strength were omitted because this strength was not recommended for approval (b) (4)
- Language describing the potential for precipitated withdrawal related to naloxone were revised to remove the statement that the symptoms are (b) (4) because at the dose of naloxone included in Bunavail, that the reaction is (b) (4) in most, but not all, individuals, and it may be aversive but not be particularly (b) (4)

- A new precaution regarding use of buprenorphine/naloxone combination products in patients with hepatic impairment was added.
- Based on a recent review of literature concerning the use of buprenorphine in pregnant and nursing women by the Maternal Health Team, revisions to the relevant sections of labeling have been made in other buprenorphine/naloxone product labels. These were incorporated into this label.
- [REDACTED] (b) (4)
- In some places, the Applicant had inserted “ [REDACTED] (b) (4) ” in text pertaining to scientific findings about the pharmacodynamics effects of sublingual administration. Because these studies were not conducted with [REDACTED] (b) (4) administration, these references were removed.
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

### 13. Decision/Action/Risk Benefit Assessment

Regulatory Action  
Approval.

#### Risk:Benefit Assessment

The Applicant filed this application as a 505(b)(2) and, therefore, is relying on the Agency’s prior finding of safety and effectiveness of another approved buprenorphine/naloxone product for their proposed indication. Subsequently, the Applicant was not required to submit the results from additional clinical trials, provided that their clinical pharmacology studies were able to demonstrate an appropriate scientific bridge. Although the safety profile due to systemic exposure was addressed by the clinical pharmacology studies, the Applicant was still required to assess their formulation’s potential for local toxicity. The results from Study BNX-201 addressed these concerns.

The Applicant also addressed the concerns that the ratio of buprenorphine to naloxone in their formulation, although different from the reference product, was nevertheless adequate to permit the naloxone to function as intended.

The review team noted that, because some transmucosal absorption of naloxone is possible, patients transitioning from full opioids at the beginning

of treatment should be initially treated for a few days with a buprenorphine-only product. Once a patient has been maintained on buprenorphine, the combination product can be introduced.

I concur with the review team that the Applicant has submitted substantial evidence to support the effectiveness and safety their product when used as directed in the accompanying label and the accompanying REMS and that the risk:benefit assessment favors approval of this application.

**Recommendation for Postmarketing Risk Management Activities**

The product will be subject to the BTOD REMS, consisting of a Medication Guide, Elements to Assure Safe Use, and Implementation System.

**Recommendation for other Postmarketing Study Commitments**

A clinical trial to assess the risk of QT prolongation with the Bunavail film.

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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.**  
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/s/  
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RIGOBERTO A ROCA  
06/06/2014