CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022410Orig1s000

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	August 21, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-410
Applicant Name	Reckitt Benckiser
Date of Submission	October 21, 2008
PDUFA Goal Date	August 21, 2009
Proprietary Name / Established (USAN) Name	Suboxone (Buprenorphine/naloxone) sublingual film
Dosage Forms / Strength	Sublingual films 2 mg/0.5 mg and 8 mg/2 mg
Proposed Indication	For the maintenance treatment of opioid dependence (b) (4)
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Elizabeth M. Kilgore, M.D.; Celia Winchell, M.D.
Statistical Review	N/A.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D. ; R. Daniel Mellon, Ph.D.
CMC Review	Xavier Ysern, Ph.D.; Ali Al-Hakim, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DDDP	Fred Hyman, D.D.S., M.P.H.; John Kelsey, D.D.S., M.B.A.; Susan Walker, M.D.
DSI	Susan Leibenhaut, M.D.; Constance Lewin, M.D.
CSS	Jian Ping, M.D., Ph.D.; Lori A. Love, M.D. Ph.D.; Michael Klein, Ph.D.
CDTL Review	Celia Winchell, M.D.
OSE/DMEPA	Zachary Oleszczuk, Pharm.D; Kellie Taylor, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DDDP=Division of Dermatology and Dental Products
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CSS=Controlled Substance Staff
CDTL=Cross-Discipline Team Leader

1. Introduction

Reckitt Benckiser has submitted this application for a line extension of and as an alternative to their Suboxone tablets which were approved in 2002. This new formulation contains buprenorphine and naloxone in a new delivery system, sublingual strips. The dosage strengths for these strips, buprenorphine 2 mg/naloxone 0.5 mg and buprenorphine 8 mg/naloxone 2 mg, are the same as the approved tablets. The sponsor purportedly created this formulation to minimize abuse and misuse, including unintended exposures in children, in addition to increasing patient compliance, minimizing counterfeiting, minimizing illegal use and diversion, and decreasing product damage during transport and storage compared to the sublingual tablets. These goals were based on the use of unit dose packaging and child-resistant packaging with improved coding. Support for the efficacy and safety of this product rests primarily on data from Phase 1 pharmacokinetic studies and reference to the sponsor's NDAs for Suboxone and Subutex.

2. Background

Buprenorphine is an opioid partial agonist which has been marketed as an injectable analgesic since 1982. Subutex (buprenorphine alone) and Suboxone were approved in 2002 for the treatment of opioid dependence. These products may only be prescribed by health care

professionals who have fulfilled certain training requirements defined in the Drug Abuse Treatment Act of 2002, which also limits the number of patients for whom a specific health care professional or group practice may prescribe these products. Due to its pharmacological properties, buprenorphine, with or without naloxone, has been thought to be useful only in patients with mild to moderate degrees of opioid dependence. Methadone remains the treatment of choice for patients with more severe forms of opioid addiction.

Recent data has shown increasing rates of abuse and diversion of Subutex and Suboxone. There is also an unexpectedly high rate of accidental exposure to children, thought to be due to the social dysfunction found in the homes of many opioid addicts. However, the number of deaths due to these accidental exposures has been low, again possibly due to the pharmacological properties of the drug.

The main concerns raised by the review team in regard to this new product are the need for an adequate REMS to mitigate the risks of abuse and accidental exposures to children, the need for finalization of the ongoing Subutex/Suboxone post-marketing study on hepatotoxicity, and better characterization of the mucosal safety of this product. While the clinical review team has determined that the hepatotoxicity study and the collection of additional data to support mucosal safety may be completed post-marketing, the REMS submitted by the sponsor in this application is not acceptable and, therefore, the application cannot be approved at this time.

3. CMC

The product is formulated as a sublingually applied film which hydrates to a gel form within about 30 seconds after application to the oral mucosa. The gel then erodes over approximately three minutes releasing the active components. A process impurity, (b) (4), was noted to have a structural alert for mutagenicity due to an (b) (4) functionality. An Ames test of this impurity was negative, but an in vitro cytogenetic assay in human lymphocytes showed it to be clastogenic at high dose levels. The sponsor has agreed to a specification limit reduction that is acceptable to the CMC and Pharmacology/Toxicology review teams.

The two dosage strengths of this product are produced from separate film formulations. The 2-mg/0.5-mg strength is produced from a low-strength formulation and the 8-mg/2-mg strength is produced form a high-strength formulation. Three different doses made from the high-strength formulation were used in the clinical studies, 12 mg/3 mg, 16 mg/4 mg, and the to-be-marketed 8 mg/2 mg. (b) (4)

However, as Dr. Winchell notes on page 7 of her review, (b) (4)

All manufacturing, testing and packaging facilities have been inspected. A twelve-month expiration period is supported by the submitted stability data.

4. Nonclinical Pharmacology/Toxicology

Three concerns were addressed by the pharmacology/toxicology review team:

1) Specifications for the clastogenic impurity [redacted] (b) (4): see discussion under Section 3.
2) In vitro studies conducted by the sponsor to assess the interaction of buprenorphine and its metabolite norbuprenorphine with several cytochrome P450 enzymes and to assess binding of buprenorphine and norbuprenorphine to benzodiazepine receptors due to the apparent increased toxicity noted in the clinical setting when Subutex or Suboxone are taken concomitantly with benzodiazepines. While there was some inhibition of cytochrome P450 enzymes at micromolar levels, the plasma concentrations of buprenorphine in the therapeutic range are unlikely to cause clinically significant inhibition of these enzymes. Neither buprenorphine nor norbuprenorphine were found to bind to either central or peripheral benzodiazepine receptors.
3) Benign Leydig cell adenomas were observed in a two-year carcinogenicity study of Suboxone in rats. Leydig cell adenomas were seen in a prior carcinogenicity study of buprenorphine alone in rats, but a mouse study was negative. These findings will be discussed in the product labeling.

5. Clinical Pharmacology/Biopharmaceutics

The following is reproduced form page 11 of Dr. Winchell's review:

> This overview of buprenorphine and buprenorphine/naloxone clinical pharmacology is taken largely from the approved labeling for NDA 20-723 and 20-733.
>
> Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both C_{max} and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the PK parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours. Naloxone does not affect the PK
>
> **Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).**

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone16 mg	Subutex 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

> 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 by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Cytochrome P-450 3A4 (CYP3A4) inhibitors may increase plasma concentrations of buprenorphine.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group. Buprenorphine is eliminated in urine (30%, primarily conjugated) and feces (69%, primarily free buprenorphine and norbuprenorphine).

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Renal impairment does not affect buprenorphine PK. The effects of renal failure on naloxone PK are unknown.

Bioequivalence of the strips compared to the tablets was evaluated in seven studies. The key results from those studies are reproduced below in tables from Dr. Winchell's review, pages 13 through 15; values outside of the standard bioequivalence limits of 80 to 120% are shown in italics:

Study 20-250-SA: 2/0.5 mg strips vs. tabs

	SL tab	***SL strip***	***Geometric Estimate***	***90% Confidence Interval***
Bup Cmax (ng/mL)	**0.78 ± 0.32**	**0.95 ± 0.27**	**121.66**	**112.62 – *131.43***
Bup AUC inf (ng*h/mL)	**7.65 ± 2.65**	**8.65 ± 2.85**	**114.22**	**106.65 – 122.32**
Nal Cmax (pg/mL)	**51.3 ± 21.1**	**54.1 ± 23.0**	**104.01**	**95.79 – 112.93**
Nal AUC inf (pg*h/mL)	**124.2 ± 52.5**	**137.3 ± 43.1**	**107.28**	**96.98 – 118.69**

Study 20-272-SA: 4/1 mg (2 x 2/0.5 mg) strips vs. tabs

	SL tab	***SL strip***	***Geometric Estimate***	***90% Confidence Interval***
Bup Cmax (ng/mL)	**1.34 ± 0.57**	**1.40 ± 0.68**	**104.61**	**94.58 – 115.69**
Bup AUC inf (ng*h/mL)	**12.46 ± 4.64**	**13.71 ± 5.88**	**104.55**	**96.42 – 113.37**
Nal Cmax (pg/mL)	**70.8 ± 34.7**	**69.8 ± 37.8**	**100.86**	**90.95 – 111.84**
Nal AUC inf (pg*h/mL)	**204.6 ± 114.9**	**204.3 ± 108.4**	**106.48**	**93.26 – 121.58**

Study 20-273-SA: 8/2 mg strips vs. tabs[1]

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**2.58 ± 1.10**	**3.37 ± 1.80**	***127.8***	**116.11 – *140.66***
Bup AUC inf (ng*h/mL)	**25.31 ± 9.50**	**30.45 ± 13.03**	**119.51**	**110.28 – *129.51***
Nal Cmax (pg/mL)	**135.0 ± 57.3**	**193.0 ± 91.2**	***141.04***	***126.87 – 156.80***
Nal AUC inf (pg*h/mL)	**374.6 ± 132.8**	**480.8 ± 201.0**	**121.19**	**108.44 – *135.44***

Study 10033995: 12/3 mg (1 x 8/2 mg + 2 x 2/0.5 mg) strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**3.44 ± 1.53**	**4.05 ± 2.63**	**115.05**	**106.44 – 124.35**
Bup AUC inf (ng*h/mL)	**37.11 ± 14.14**	**40.50 ± 15.93**	**111.21**	**105.62 – 117.09**
Nal Cmax (pg/mL)	**170.0 ± 77.6**	**207.0 ± 143.0**	**117.24**	**106.80 – *128.71***
Nal AUC inf (pg*h/mL)	**524.0 ± 253.6**	**582.7 ± 324.9**	**110.47**	**102.90 – 118.60**

[1] DSI concluded that "Accuracy of the reported naloxone concentrations for subjects 407 (Period 2) and 443 (all periods) has not been assured due to unresolved chromatographic interference in at least half the reportable naloxone values in each period. The naloxone data for these periods should be omitted and bioequivalence should be re-evaluated." A reevaluation was performed by Dr. Agarwal. However, because bioequivalence was not previously established for naloxone in this study, the effect of this reanalysis would be unlikely to change the conclusions about the application. [*Indeed, Dr. Agarwal's reevaluation did demonstrate that the data remained supportive in spite of the DSI findings.*]

Study 20-A90-AU: 16/4 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**4.51 ± 1.51**	**5.47 ± 1.99**	***133.64***	**117.52 – *151.98***
Bup AUC inf (ng*h/mL)	**47.31 ± 13.81**	**58.53 ± 20.59**	***132.50***	**120.63 – *145.54***
Nal Cmax (pg/mL)	**259.0 ± 200.0**	**324.0 ± 231.0**	***143.79***	**116.86 – *176.92***
Nal AUC inf (pg*h/mL)	**677.7 ± 366.4**	**930.4 ± 421.3**	***137.71***	**121.19 – *156.49***

Study 20-291-SA: Dose proportionality of the 2/0.5, 2 x 2/0.5, 8/2, 12/3 and 16/4 mg strips
Buprenorphine

	2/0.5	**2*2/0.5**	**8/2**	**12/3**	**16/4**
Cmax (ng/mL)	**1.07**	**1.66**	**3.55**	**4.80**	**6.05**
AUClast (hr*ng/mL)	**7.18**	**13.42**	**28.71**	**39.86**	**50.32**
AUCinf (hr*ng/mL)	**8.43**	**14.62**	**30.66**	**41.74**	**53.40**

Naloxone

	2/0.5	**2*2/0.5**	**8/2**	**12/3**	**16/4**
Cmax (pg/mL)	**48.5**	**72.8**	**193**	**286**	**401**
AUClast (hr*pg/mL)	**100.6**	**164.1**	**442.9**	**647.5**	**937.9**
AUCinf (hr*pg/mL)	**105.1**	**171.0**	**454.8**	**665.1**	**958.4**

There are "high-side" failures for all comparisons, most prominently for the higher strength strips. However, there were no new safety concerns noted in the clinical database for subjects using these strips and the safety of doses of up to 24 mg/day of the Suboxone tablets is supported by the application for that product, a reference listed drug for this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No new efficacy data was submitted in support of this application. The sponsor is depending on their 505(b)(2) reference which is acceptable.

8. Safety

There were 126 subjects exposed for 12 weeks to any dose of the study drug. Fewer than 80 of those subjects were dosed within the labeled range of 12 to 16 mg; however, patients can be maintained on lower doses of the tablets, so this data base is acceptable. Dr. Winchell raises a concern regarding the fact that the subjects in the clinical studies were prescribed and/or self administered drug in multiple divided doses, in contrast to the labeled single daily dosing regimen. A survey by the sponsor also found this practice occurring with Suboxone prescribing and use. Dr. Winchell notes that, single daily dosing is thought to assist in extinguishing the behavior of self-administration that occurs in addiction and that, indeed, there is a substantial literature advocating dosing on a less than daily basis for this reason. The REMS for this product will need to fully address appropriate dosing for prescribers and include statements related to proper use in the MedGuide for patients.

There were no serious or unexpected safety signals found in the clinical data base for the studies of this new formulation. However, oral mucosal irritation did appear to occur with much greater frequency compared to the tablet formulation. While the main safety study for this application did not identify any treatment-related safety issues related to the mouth, Dr. Winchell notes that that study may not have been appropriately conducted to do so. In addition, the clinical pharmacology studies and a small, inpatient induction study did suggest the strips may be associated with mild oral irritation. Another possible complication related to assessing the oral tolerability of the product is that the strips were not used in the clinical study in the manner outlined in the proposed product label. However, based on his review of the studies, Dr. Hyman drew the following conclusions (pages 5 and 6 of this review):

> It is the recommendation of this reviewer that the difference between the sponsor's planned application (b) (4) versus the actual application in the clinical trials to the floor of the mouth, under the tongue will not invalidate the safety results of the clinical trials. However, the printed directions for use should reflect the actual placement during the clinical trials. In particular, the illustration in the Medication Guide section of the labeling should be replaced with one that reflects the actual use during the clinical trials; also the description of placement for the second FS as (b) (4) should be avoided. Should the sponsor wish to label the drug to (b) (4) clinical studies should be repeated in that manner to test for ease of use, and any oral irritation that could result from this application.

The sponsor has agreed to change the labeled administration instructions to appropriately reflect how the product was used in the clinical studies.

The clinical review team had raised concerns regarding precipitated withdrawal in the opioid dependent patients who would be treated with this product. Although Dr. Winchell expressed some discomfort with the one study specifically designed to evaluate this potential, she concluded that the results were generally not concerning. The incidence of withdrawal symptoms in the overall database was no higher than would be expected in this population.

Hepatic toxicity has been seen in the post-marketing data for Suboxone. While no new or increased signal was noted in the database for this product, Dr. Winchell has recommended that the post-marketing study commitment to evaluate the comparative effects of buprenorphine and methadone on the liver should be reiterated, but this time as a post-marketing requirement. I concur with this recommendation.

9. Advisory Committee Meeting

The review team determined that an advisory committee meeting was unnecessary for this new formulation of buprenorphine/naloxone as there were no clinically serious new or unexpected safety concerns specific to this product.

10. Pediatrics

This product is exempt from the pediatric study requirements authorized by PREA as the sponsor received orphan designation for the active moiety of buprenorphine, with or without naloxone, for the treatment of opioid addiction.

11. Other Relevant Regulatory Issues

There are no other outstanding regulatory issues.

12. Labeling

The labeling has been provisionally revised from the reference listed drug's label in several ways. It emphasizes more strongly the abuse potential of the drug and the risk of accidental pediatric exposure and includes more explicit recommendations on clinical management in the dosing and administration section. A final label will require further discussion with the sponsor and include appropriate references to the product's REMS.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Complete Response

- Risk Benefit Assessment

  The sponsor has demonstrated that this new formulation of buprenorphine and naloxone is safe and effective when used according to the labeled instructions, and that the product quality is acceptable. However, they will need to provide an adequate REMS to address the Agency's concerns regarding misuse and abuse of the product and, therefore, I am unable to approve the application at this time.

- Required Post-marketing Risk Evaluation and Mitigation Strategy

  In order to assure that the benefits of this product outweigh the risks of abuse, misuse and accidental pediatric exposure, the Agency has determined that the product must have a REMS comprised of a MedGuide, an Element to Assure Safe Use (ETASU), and a timetable for submission of assessments of the REMS. The ETASU falls under section 505-1(f)(3)(E) of the FDCA and is intended to ensure that 1) each patient is receiving the psychosocial support necessary for safe and effective use buprenorphine, 2) each patient adheres to the conditions of safe use explained to him/her, and 3) each patient is using Suboxone sublingual film appropriately and making adequate progress towards treatment goals.
  .

- Required Post-marketing Study Requirements

  As we are unable to approve this application at this time, we will continue to work with the sponsor to assure completion of their ongoing study designed to evaluate the comparative effects of buprenorphine and methadone on the liver. Should that study not be completed at the time this application is ready for approval, we will change it from a post-marketing commitment to a post-marketing requirement.

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

/s/

BOB A RAPPAPORT
08/21/2009

Addendum to Cross-Discipline Team Leader Review

Date	8/10/09
From	Celia Winchell, M.D., Clinical Team Leader
Subject	Addendum to Cross-Discipline Team Leader Review: Resolution of Concerns Regarding Methods of Administration of the Proposed Product
NDA #	22-410
Applicant	Reckitt Benckiser
Date of Submission	Letter Date: 10/20/08 Stamp Date: 10/21/08
PDUFA Goal Date	8/21/09
Proprietary Name / Established (USAN) names	**<TRADENAME TBA>** **(buprenorphine and naloxone) sublingual film** 2 mg/0.5 mg and 8 mg/2 mg
Dosage forms / Strength	Buprenorphine 2 mg with Naloxone 0.5 mg Buprenorphine 8 mg with Naloxone 2 mg
Proposed Indication(s)	Maintenance Treatment of Opioid Dependence (b) (4)

At the time my Cross-Disciplinary Team Leader Review was finalized (7/10/09, to meet Good Review Management Practices timetable requirements), there was a new issue which was described as unresolved. This memo documents the resolution of that issue.

At that time, it had recently come to our attention that there were potentially clinically significant discrepancies among the sponsor's recommended method of administration (in proposed labeling), the method of administration in the clinical pharmacology program, and the method of administration in the clinical safety study. The patient labeling submitted in late June contained an illustration making it clear that the product was to be applied (b) (4). None of the directions in the clinical studies appear to have communicated this clearly. The clinical pharmacology studies used complicated wording that was difficult to interpret but did not convey the concept illustrated in the proposed labeling; the clinical safety study used directions which implied that the product should be placed on the floor of the mouth.

We obtained information from Reckitt Benckiser regarding how the products were actually administered in the clinical studies. Using photographs illustrating the oral cavity, the investigators indicated the location that the study drug was placed by their subjects. Although Reckitt Benckiser's interpretation of the photographs was

(b) (4)

(b) (4)

However, the interpretation of the review staff of the photographs sent was that the investigators indicated that the product was placed in the floor of the mouth.

We requested that the Division of Dermatology and Dental Products (DDDP) provide an assessment of the potential impact of various administration methods, and an opinion on whether the data from the studies provides support for the use of the product as proposed in labeling. Dr. Frederick Hyman of DDDP noted that

> [A]ccording to the descriptions of the placement as provided in the protocols, as well as the photographs that were taken during the trials that showed the placement, the strips were placed on the floor of the mouth. The sponsor's proposed labeling includes (b) (4) Instead, the instructions should reflect the actual use during the trial.
>
> …
>
> It is the recommendation of this reviewer that the difference between the sponsor's planned application (b) (4) versus the actual application in the clinical trials to the floor of the mouth, under the tongue will not invalidate the safety results of the clinical trials. However, the printed directions for use should reflect the actual placement during the clinical trials.

The Clinical Pharmacology team was also been asked to comment on the potential impact of different administration methods on the pharmacokinetics, to determine whether the PK studies were conducted in a manner that provides information about the PK when the product is used as proposed in labeling. Dr. Sheetal Agarwal provided the following comments.

> As a matter of general understanding and use of terminology, sublingual administration means that the drug product is placed underneath the tongue. In this case, the product will rest on the floor of the mouth (b) (4) The sublingual film strips are formulated to dissolve rapidly. Upon contact with the oral mucosa, the strips hydrate rapidly forming a hydrophilic gel which then erodes in a period of about three minutes. So, dissolution is not a rate limiting step with the sublingual strips

(b) (4)

> and the exact placement of the strip and any folding or bending of the strips should not significantly alter the dissolution rate…. Although not sought for approval, sponsor tested the buccal mode of administration as well in several of the PK studies. Although not reviewed in detail, a quick overview of the studies showed …these two routes of administration yielded similar bioavailability [lending] further comfort that any bioavailability differences resulting from the potentially different ways in which the sublingual strips may have been used in the NDA database may not be clinically significant.

(b) (4)

No diagram or illustration is likely to be required to help patients understand this placement, it is the placement that was actually used in both clinical pharmacology and safety studies, and upon which all of the data submitted to this application was based.

Reckitt Benckiser has agreed to amend the directions and proposes the following alternative set of directions, which appear basically acceptable but have not yet been reviewed by the OSE personnel with expertise in patient communication.

(b) (4)

This issue is therefore resolved by the modification of the labeling to match the way the product was actually tested.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22410	ORIG 1		SUBOXONE (BUPRENORPHINE/NALOXONE)

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

/s/

CELIA J WINCHELL
08/10/2009

Cross-Discipline Team Leader Review

Date	7/10/09
From	Celia Winchell, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA #	22-410
Applicant	Reckitt Benckiser
Date of Submission	Letter Date: 10/20/08 Stamp Date: 10/21/08
PDUFA Goal Date	8/21/09
Proprietary Name / Established (USAN) names	**<TRADENAME TBA>** **(buprenorphine and naloxone) sublingual film** 2 mg/0.5 mg and 8 mg/2 mg
Dosage forms / Strength	Buprenorphine 2 mg with Naloxone 0.5 mg Buprenorphine 8 mg with Naloxone 2 mg
Proposed Indication(s)	Maintenance Treatment of Opioid Dependence ((b) (4)
Recommended:	Complete Response

1 Introduction

This is a New Drug Application for buprenorphine and naloxone soluble film for sublingual administration. (n.b. the proposed proprietary name, "Suboxone (b) (4) was deemed unacceptable by the Office of Surveillance and Epidemiology (OSE); nevertheless the product will be referred to by that name in this review for convenience and clarity). Suboxone (b) (4) is intended for the maintenance treatment of opioid dependence, and was developed as an alternative to Suboxone sublingual tablets (NDA 20-733, approved October 8, 2002). The dosage strengths of Suboxone (b) (4) for which marketing approval is being sought are the same as those currently approved for Suboxone sublingual tablets, and are as follows:

- Buprenorphine 2mg With Naloxone 0.5mg (herein referred to as 2/0.5 or as 2 mg)
- Buprenorphine 8mg With Naloxone 2mg (herein referred to as 8/2 or as 8 mg)

The film formulation is intended by the Applicant to be similar in efficacy to Suboxone sublingual tablets, while offering additional safety and increased compliance. Reckitt Benckiser reports that the formulation was "created for the purpose of minimizing abuse and misuse of the product, including unintended and potentially dangerous exposure in children." Other stated goals include increasing patient compliance, minimizing counterfeiting, minimizing illegal use and diversion, and decreased product damage during transport and storage compared to sublingual tablets. The achievement of these goals is based on the use of a unit dose product and package that is child-resistant, has enhanced physical integrity, and improved coding.

The NDA rests primarily on a program of Phase 1 pharmacokinetic (PK) studies evaluating bioavailability, dose proportionality, and comparisons to Suboxone tablets, and on previous Reckitt Benckiser data submitted to the NDAs for Suboxone and Subutex tablets, encompassing data on safety and efficacy of buprenorphine sublingual solution, Suboxone and Subutex. A small open-label safety study of Suboxone (b) (4) and a small laboratory study comparing Suboxone (b) (4) to a buprenorphine-only film strip supplements these findings. No new efficacy studies were conducted for this NDA.

2 Background

Buprenorphine HCl is a narcotic analgesic which has been marketed since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain. In 2002, two sublingual tablet formulations were approved for the treatment of opioid dependence: Subutex (buprenorphine only, NDA 20-732) and Suboxone (buprenorphine with naloxone intended to deter abuse[1], NDA 20-733). The present NDA proposes a new dosage form of the buprenorphine/naloxone combination product, in a soluble strip intended for sublingual use. The application is based on five sources of information:

1. Pharmacokinetic studies in naltrexone-blocked healthy volunteers, comparing the new product to the approved products.
2. Reference to efficacy and safety information included in Reckitt Benckiser's approved applications for Subutex and Suboxone.
3. A single open-label safety study in patients already using Suboxone, intended to evaluate the local tolerability of the new formulation, because no previous experience with sublingual film strips is available to establish the safety of this dosage form.
4. A small inpatient laboratory study comparing the initiation of dosing with Suboxone (b) (4) to initiation of dosing with a buprenorphine-only film strip.
5. Post-marketing data and literature regarding buprenorphine products.

Reckitt Benckiser makes the following assertions about the benefits of the proposed product, including (applicant's language quoted below):

> • Use of child-resistant packaging in unit dose format for additional protection against unintentional pediatric exposure,
> • Protection against counterfeiting,
> • Protection against diversion, by providing a dosage form that is very difficult for the patient to remove from the sublingual mucosa once it is administered. This will provide assurance to the caregiver that the dose has actually been taken appropriately in a supervised setting.
> • Improved patient convenience,
> • Provision of a robust unit dose product for hospital and institutional use,
> • Decreased product damage during shipping as compared to Suboxone tablets

These claims will be addressed in the review below as appropriate. Briefly, accidental pediatric exposure is a concern for the buprenorphine sublingual tablets currently marketed. There is potential for child-resistant, unit-of-use packaging to be beneficial in this regard. However, as will be discussed below, the Applicant has reported that it is common for patients to divide their doses into fractions for use. Therefore, partial doses left out of the child-resistant packaging may still represent a risk. Furthermore, the more rapid dissolution of this dosage form compared to the tablets, and the difficulty of spitting it out once it is placed in the mouth, could actually contribute to more severe outcomes when the product is accidentally taken by a small child.

[1] Naloxone is poorly bioavailable by the sublingual route and expected to be inactive under usual conditions of use. The inclusion of naloxone with buprenorphine in the Suboxone product is designed to reduce the intravenous abuse potential of the product compared to a buprenorphine only product by precipitating withdrawal if used intravenously by individuals physically dependent on full agonists.

Regarding protection against diversion in supervised settings via removal from the mouth, Suboxone is not generally administered in a supervised setting after initial stabilization of patients, and "cheeking" of medication is not identified as a source of diverted medication; therefore the difficulty of removing the product from the mouth once administered is unlikely to have any discernible effect on diversion of this product.

Regarding patient convenience, the doses proposed for marketing in this application are only the 2 mg buprenorphine/0.5 mg naloxone strip and the 8 mg buprenorphine/2 mg naloxone strip, representing little clinical improvement over the existing products other than more rapid dissolution.[2]

[2] Reckitt Benckiser initiated development programs for (b) (4) buprenorphine/naloxone combination strips. (b) (4) four doses, containing 2 mg, 8 mg, 12 mg, and 16 mg of buprenorphine respectively, were tested clinically. The approved products are available only in tablets containing 2 mg or 8 mg of buprenorphine. The dose recommended in labeling for the sublingual tablets is 16 mg/day as a single daily dose and requires dosing with two 8 mg tablets simultaneously. Therefore, the availability of higher doses would have contributed to patient convenience and may have reduced diversion, but these higher doses were not ultimately proposed for marketing.

3 CMC/Device

3.1 General product quality considerations

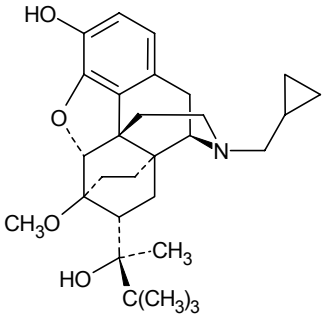
The Chemistry, Manufacturing, and Controls (CMC) review was performed by Dr. Xavier Ysern, Ph.D.

The drug product, Suboxone (b) (4) (buprenorphine and naloxone) sublingual film, a pale orange 0.875" x 0.5"soluble film strip which reportedly "hydrates readily to a gel form (within about 30 seconds) upon application to the oral mucosa [with] subsequent erosion over approximately three minutes," consists of two drug substances, buprenorphine hydrochloride and naloxone hydrochloride. There are no novel excipients.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water. Chemically, buprenorphine is 17-(cyclopropylmethyl)-α -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]-.

Buprenorphine hydrochloride has the molecular formula C29 H41 NO4 HCl and the molecular weight is 504.10.

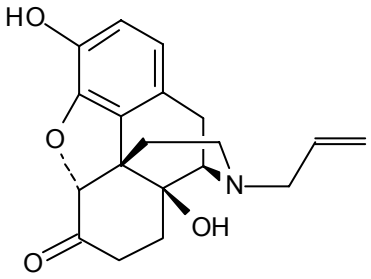
Structural Formula of Buprenorphine



.HCl

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride. Naloxone hydrochloride has the molecular formula C19 H21 NO4 HCl .2H2 O and the molecular weight is 399.87.

Structural Formula of Naloxone



.HCl • $2H_2O$

There is one process impurity, [redacted], which was found to have a structural alert associated with the [redacted] functionality during the review of a new drug application for Suboxone (NDA 20-733). Two mutagenicity studies have been performed; an Ames test was negative (non-mutagenic) and an in vitro cytogenetic assay in human lymphocytes showed [redacted] to be weakly clastogenic at high dose levels. As a consequence of these results the specification limit for the [redacted] content of naloxone has been reduced from [redacted] a level agreed with FDA as part of the approval commitment for 20-733.

Buprenorphine HCl is manufactured by Reckitt Benckiser (Drug Master File, DMF # 12412) and naloxone HCl is manufactured by [redacted] (DMF # [redacted]) and by [redacted] (DMF # [redacted]). [redacted] is the current manufacturer of naloxone used in the manufacture of Suboxone sublingual tablets. Chemistry, manufacturing and controls for the above two compounds are described in the corresponding DMFs. Letters of authorization have been adequately provided and the DMFs have been reviewed and found acceptable.

The two dosage strengths of buprenorphine and naloxone soluble films are produced from separate film formulations. A low strength film formulation is used to produce the Suboxone [redacted] 2 mg/ 0.5 mg dose strength and a high strength film formulation is used to produce the Suboxone [redacted] 8 mg/ 2 mg dosage strength product. The soluble films are 0.875" x 0.5" for both dose strengths. The weights of the 2 mg/0.5 mg and 8 mg/2 mg soluble films are 40 mg and 50 mg respectively. For the 12 mg and 16 mg doses used in the clinical trials (but not proposed for marketing) the buprenorphine /naloxone 8/2mg film strip buffered to pH 3 was utilized to produce the two higher strength film strips by cutting the bulk film to longer length film pieces.

This is significant because the clinical trials were conducted with one dose of the low-strength film (2 mg/0.5 mg) but three different doses of the high-strength films (8 mg/2 mg; 12 mg/3 mg; and 16 mg/4 mg). However, only one of these three is proposed for marketing (8 mg/2 mg). [redacted]

(b) (4)

3.2 Facilities review/inspection

Facilities inspection was requested for 8 sites and has been completed for 7. The inspection of the drug substance manufacturing, release testing, and stability testing site in Hull, England, has not been completed and is scheduled for 7/22/09. This site was included in the NDA for 20-732 and 20-733 but has not been inspected recently enough to find it acceptable based on profile.

A recommendation of "withhold" was made for the finished dosing packaging site, (b) (4) , but Reckitt Benckiser has indicated that they plan to withdraw this site and will not be packaging the product at this site. An alternate site was submitted and has been found acceptable.

All other sites have been found acceptable.

3.3 Stability

Dr. Ysern has concluded that the stability data supports 12 month expiration period.

3.4 Other notable issues: Packaging and Labeling Process

Reckitt Benckiser's original manufacturing process involved (b) (4) . They may choose, as an alternative, to submit it as a post-approval change.

As of this writing, Reckitt Benckiser has not submitted this proposal and seems to have elected not to do so to avoid delaying the action on this application.

4 Nonclinical Pharmacology/Toxicology

The review of nonclinical pharmacology/toxicology was conducted by Elizabeth Bolan, Ph.D. Much of the text below is excerpted from her review.
The majority of the nonclinical data relied upon in NDA 22-410 for Suboxone (b) (4) is found in NDAs 20-732 (Subutex) and 20-733 (Suboxone). Three new issues were addressed in the pharmacology/toxicology review: levels of a clastogenic impurity; new *in vitro* data on the interaction of buprenorphine and metabolites with microsomal enzymes and benzodiazepine receptors; and a carcinogenicity study with Suboxone.

4.1 Specifications for clastogenic impurity

The naloxone drug substance contains (b) (4)), an impurity with a structural alert for mutagenicity. As a post approval commitment for Suboxone (NDA 20-733), the Division requested adequate qualification of (b) (4). In studies submitted to this NDA, (b) (4) was not mutagenic in the Ames test but was found to be clastogenic in an in vitro cytogenetic assay in human lymphocytes. Because of the positive finding for clastogenicity, the levels of (b) (4) in the drug substance should be reduced to the currently acceptable threshold for known genotoxic impurities of NMT (b) (4) mcg/day. The specification set by the Applicant for (b) (4) would result in levels NMT (b) (4) mcg/day when Suboxone (b) (4) is used as labeled, and are therefore acceptable.

4.2 In vitro studies

Reckitt Benckiser has conducted an *in vitro* study assessing the interaction of buprenorphine and its metabolite norbuprenorphine with several cytochrome P450s in human liver and in cDNA expressed microsomes. At micromolar levels, buprenorphine inhibited CYP2D6 and CYP3A and nor-buprenorphine inhibited CYP2D6. However, plasma concentrations of buprenorphine in the therapeutic range are unlikely to cause clinically significant inhibition of CYP2D6 or CYP3A in patients.

Data were also submitted showing that buprenorphine and nor-buprenorphine do not bind to either central or peripheral benzodiazepine receptors. Although an interaction between benzodiazepines and buprenorphine has been noted (suggesting potentiation of toxicity), the mechanism for this interaction remains unknown, in light of data submitted it is most likely not due to PK interactions or direct action of BUP or nor-BUP on central or peripheral benzodiazepine receptors.

4.3 Carcinogenicity

A 2-year carcinogenicity study with Suboxone was conducted in the rat using doses yielding human exposure margins of 4, 18 and 44 times the human sublingual dose of 16/4 mg buprenorphine/naloxone (based on buprenorphine AUC values). Treatment-related unilateral benign Leydig cell (testes) adenomas were observed at the high dose and bilateral benign Leydig cell adenomas were observed at all doses. No other treatment-related neoplasms were observed in males and no treatment-related neoplasms were observed in females.

This study confirms the findings of Leydig cell tumors that were seen in a prior carcinogenicity assessment in rats conducted with buprenorphine alone for the Subutex NDA. The findings of Leydig cell tumors from the buprenorphine study as well as negative findings from a mouse carcinogenicity study with buprenorphine are described in the current Suboxone/Subutex label.

The results from the Suboxone carcinogenicity study as well as the buprenorphine rat and mouse studies will be included in the Suboxone (b) (4) label. It is recommended that the Suboxone/Subutex label be updated to include results from the Suboxone carcinogenicity study.

5 Clinical Pharmacology/Biopharmaceutics

5.1.1 General Background

This overview of buprenorphine and buprenorphine/naloxone clinical pharmacology is taken largely from the approved labeling for NDA 20-723 and 20-733.

Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both C_{max} and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the PK parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours. Naloxone does not affect the PK

Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone16 mg	Subutex 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

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 by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Cytochrome P-450 3A4 (CYP3A4) inhibitors may increase plasma concentrations of buprenorphine.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group. Buprenorphine is eliminated in urine (30%, primarily conjugated) and feces (69%, primarily free buprenorphine and norbuprenorphine).

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Renal impairment does not affect buprenorphine PK. The effects of renal failure on naloxone PK are unknown.

5.1.2 Clinical Pharmacology Data Reviewed

This application rests primarily on pharmacokinetic linkage of the proposed product to the approved product. The Clinical Pharmacology package submitted for this NDA consisted of 19 Phase 1 pharmacokinetic (PK) studies conducted in healthy adult volunteers (including pilot, pivotal bioequivalence (BE) and dose and dosage form proportionality studies, studies with other strengths of Suboxone (b) (4) that are not sought for approval, (b) (4)

(b) (4)). Out of the 19 PK studies submitted, 7 were deemed relevant for this NDA and were reviewed. Out of the 7 studies reviewed, 4 were thoroughly reviewed because they form the basis of approval for the subject matter of this NDA and the other 3 are considered additional supportive studies. The other 10 PK studies submitted included testing of (b) (4) and the buccal route of administration for (b) (4) the (b) (4) Suboxone (b) (4).

The seven relevant studies include studies comparing one dose of strip to a comparable dose of Suboxone tablet (20-250-SA and 20-273-SA), studies comparing various combinations to yield intermediate doses such as 4 mg (2 x 2 mg) or 12 mg (8 mg plus 2 x 2 mg), somewhat less-relevant studies of the doses not proposed for marketing (12 mg and 16 mg strips) compared to equivalent doses of tablets, and a dose-proportionality study of various doses of Suboxone (b) (4). These are listed below.

- Study 20-250-SA: 2/0.5 mg strips vs. tabs
- Study 20-273-SA: 8/2 mg strips vs. tabs
- Study 20-272-SA: 2 x 2/0.5 mg strips vs. tabs
- Study 10033995: 1 x 8/2 mg + 2 x 2/0.5 mg strips vs. tabs
- Study 20-B90-SA: 12/3 mg strips vs. tabs
- Study 20-A90-AU: 16/4 mg strips vs. tabs
- Study 20-291-SA: Dose proportionality of the 2/0.5, 2 x 2/0.5, 8/2, 12/3 and 16/4 mg strips

In these studies, the protocol called for the tablets to be placed by research staff "in the mid portion of the sublingual space."

In the tables below, Dr. Agarwal summarizes the Cmax and AUC data for each study[3] and provides a 90% confidence estimate of the relative bioavailability. Note that the criteria for bioequivalence (confidence estimate falling between 80-120%) is not met in several studies. Buprenorphine exceeds criteria for BE limits in several studies; naloxone exceeds criteria to a greater degree. Values outside these limits are shown in the tables below using italics.

(b) (4)

Study 20-250-SA: 2/0.5 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**0.78 ± 0.32**	**0.95 ± 0.27**	**121.66**	**112.62 – *131.43***
Bup AUC inf (ng*h/mL)	**7.65 ± 2.65**	**8.65 ± 2.85**	**114.22**	**106.65 – 122.32**
Nal Cmax (pg/mL)	**51.3 ± 21.1**	**54.1 ± 23.0**	**104.01**	**95.79 – 112.93**
Nal AUC inf (pg*h/mL)	**124.2 ± 52.5**	**137.3 ± 43.1**	**107.28**	**96.98 – 118.69**

Study 20-272-SA: 4/1 mg (2 x 2/0.5 mg) strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**1.34 ± 0.57**	**1.40 ± 0.68**	**104.61**	**94.58 – 115.69**
Bup AUC inf (ng*h/mL)	**12.46 ± 4.64**	**13.71 ± 5.88**	**104.55**	**96.42 – 113.37**
Nal Cmax (pg/mL)	**70.8 ± 34.7**	**69.8 ± 37.8**	**100.86**	**90.95 – 111.84**
Nal AUC inf (pg*h/mL)	**204.6 ± 114.9**	**204.3 ± 108.4**	**106.48**	**93.26 – 121.58**

Study 20-273-SA: 8/2 mg strips vs. tabs[4]

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**2.58 ± 1.10**	**3.37 ± 1.80**	***127.8***	**116.11 – *140.66***
Bup AUC inf (ng*h/mL)	**25.31 ± 9.50**	**30.45 ± 13.03**	**119.51**	**110.28 – *129.51***
Nal Cmax (pg/mL)	**135.0 ± 57.3**	**193.0 ± 91.2**	***141.04***	***126.87 – 156.80***
Nal AUC inf (pg*h/mL)	**374.6 ± 132.8**	**480.8 ± 201.0**	**121.19**	**108.44 – *135.44***

Study 10033995: 12/3 mg (1 x 8/2 mg + 2 x 2/0.5 mg) strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**3.44 ± 1.53**	**4.05 ± 2.63**	**115.05**	**106.44 – 124.35**
Bup AUC inf (ng*h/mL)	**37.11 ± 14.14**	**40.50 ± 15.93**	**111.21**	**105.62 – 117.09**
Nal Cmax (pg/mL)	**170.0 ± 77.6**	**207.0 ± 143.0**	**117.24**	**106.80 – *128.71***
Nal AUC inf (pg*h/mL)	**524.0 ± 253.6**	**582.7 ± 324.9**	**110.47**	**102.90 – 118.60**

Study 20-A90-AU: 16/4 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**4.51 ± 1.51**	**5.47 ± 1.99**	***133.64***	**117.52 – *151.98***
Bup AUC inf (ng*h/mL)	**47.31 ± 13.81**	**58.53 ± 20.59**	***132.50***	**120.63 – *145.54***
Nal Cmax (pg/mL)	**259.0 ± 200.0**	**324.0 ± 231.0**	***143.79***	**116.86 – *176.92***
Nal AUC inf (pg*h/mL)	**677.7 ± 366.4**	**930.4 ± 421.3**	***137.71***	**121.19 – *156.49***

[4] DSI concluded that "Accuracy of the reported naloxone concentrations for subjects 407 (Period 2) and 443 (all periods) has not been assured due to unresolved chromatographic interference in at least half the reportable naloxone values in each period. The naloxone data for these periods should be omitted and bioequivalence should be re-evaluated." This reevaluation is being performed by Dr. Agarwal. However, because bioequivalence was not previously established for naloxone in this study, the effect of this reanalysis would be unlikely to change the conclusions about the application.

Study 20-291-SA: Dose proportionality of the 2/0.5, 2 x 2/0.5, 8/2, 12/3 and 16/4 mg strips
Buprenorphine

	2/0.5	2*2/0.5	8/2	12/3	16/4
Cmax (ng/mL)	**1.07**	**1.66**	**3.55**	**4.80**	**6.05**
AUClast (hr*ng/mL)	**7.18**	**13.42**	**28.71**	**39.86**	**50.32**
AUCinf (hr*ng/mL)	**8.43**	**14.62**	**30.66**	**41.74**	**53.40**

Naloxone

	2/0.5	2*2/0.5	8/2	12/3	16/4
Cmax (pg/mL)	**48.5**	**72.8**	**193**	**286**	**401**
AUClast (hr*pg/mL)	**100.6**	**164.1**	**442.9**	**647.5**	**937.9**
AUCinf (hr*pg/mL)	**105.1**	**171.0**	**454.8**	**665.1**	**958.4**

In summary, the lower strength film (used to make the 2 mg/0.5 mg Suboxone strip) is bioequivalent (BE) to the 2 mg/0.5 mg Suboxone tablet, but the higher strength film, as 8 mg/1 mg Suboxone (b) (4) does not appear to be BE to the 8 mg/1 mg Suboxone tablet. The high-side failure is particularly notable when one 16 mg strip ((b) (4) is compared to two 16 mg tablets. (b) (4) At this dose, the mean AUC and Cmax are 30-40% higher than for the tablet. My clinical impression is that dose adjustment might be necessary for patients transitioning between products, although the existing safety database including data from the sublingual solution studies still provides support for use of this more bioavailable product at the currently-labeled doses. However, dosing up to 24 mg/day is still supported by the data in the referenced applications, where buprenorphine sublingual solution was used. There is no direct support for the highest potential exposure to naloxone other than the data in this application, because the highest tablet dose of Suboxone in the referenced application 20-733 was 24 mg/day.

6 Clinical Microbiology

(n/a)

7 Clinical/Statistical- Efficacy

No new efficacy studies were included in this application. There was no statistical review of the clinical data.

The efficacy data and recommendations for dosing are based on the approved application for Suboxone. A summary of the efficacy studies supporting that application is included in Appendix 9.3 of the Clinical Review. Briefly, the application rested on two studies of buprenorphine sublingual solution that demonstrated the efficacy of an 8 mg/day dose of buprenorphine sublingual solution, which was roughly equivalent to a 12 mg/day dose delivered in a tablet formulation. A single, four week, placebo-controlled study using the buprenorphine/naloxone combination tablet demonstrated that the dosing regimen (8 mg buprenorphine tablet on day one, 2 x 8 mg buprenorphine tablet on day two, and 2 x 8 mg buprenorphine/naloxone combination tablet thereafter) was effective. These three studies taken together were considered sufficient to support approval of the buprenorphine/naloxone sublingual tablet, Suboxone. Open-label safety studies involving dosing up to 32 mg/day of solution and up to 24 mg/day of Suboxone tablets were also included in the referenced applications. No new efficacy studies have been submitted to support the approval of the Suboxone film strip, as Reckitt Benckiser hoped to demonstrate bioequivalence or (once bioequivalence was not demonstrated for all strengths) argue that the differences between the tablet and film strip products were of no clinical significance.

It should be noted that we alerted Reckitt Benckiser to concerns that higher bioavailability of the naloxone component in the film strip formulation compared to the Suboxone tablet could raise concerns about efficacy. This is because naloxone, although poorly bioavailable orally and sublingually and theoretically inactive when the product is used as directed, is absorbed to some degree sublingually and could potentially precipitate withdrawal in opioid-dependent patients. However, because buprenorphine binds with high affinity to the opioid receptor, it has been noted that naloxone does not compete effectively with buprenorphine. (Initial attempts to induce naloxone-precipitated withdrawal in buprenorphine-dependent animals and humans were unsuccessful, leading to the misleading conclusion that buprenorphine did not produce dependence. Very high doses of naloxone are required to reverse the effects of buprenorphine.) Therefore, patients dependent on buprenorphine are unlikely to be vulnerable to precipitation of withdrawal by naloxone. The clinical study of Suboxone relied upon for approval of the tablet formulation used Subutex for the initial two days of treatment, so that patients were not transitioned directly from full agonists to the combination product. (b) (4) Notably, the product was studied only in patients already stabilized on buprenorphine and the proposed labeling also stipulates that it is not intended for initial treatment. This is intended to finesse the question of whether the higher naloxone plasma levels seen after sublingual film strip use compared to Suboxone will create an important clinical difference with regard to efficacy.

8 Safety

8.1 Overview

In summary, safety data from approximately 75 patients treated at or above the generally-recommended daily dose for 12 weeks was provided, although virtually none of these used the product at the dose regimen recommended in labeling (a single daily dose of 16 mg/day). Although no major safety concerns were identified, the quality of the main safety study was questionable and data from other studies in the application suggest that this formulation may be more irritating to the oral mucosa than the tablet.

8.2 Background

In pre-submission interactions with the Agency, Reckitt Benckiser was informed that a safety database of at least 100 subjects exposed to the to-be-marketed product in a study focused on safety, with an emphasis on local tolerability. We also raised concerns about the possibility of precipitated withdrawal due to the higher bioavailability of naloxone. (Higher bioavailability of buprenorphine may also contribute to precipitation of withdrawal in some patients.)

In addition, we asked Reckitt Benckiser to revisit certain safety questions which were to be evaluated as Phase 4 commitment studies at the time of approval of the referenced applications for the sublingual tablets, notably the possibility that buprenorphine could have adverse hepatic effects, particularly in subjects with viral hepatitis.

The safety review for this application focused on:

1. Data generated in Reckitt Benckiser's safety study, RB-US-07-0001
2. Data generated in Reckitt Benckiser's laboratory induction study, RB-US-07-0002
3. Reckitt Benckiser's comprehensive evaluation of hepatic safety issues, comprising their evaluation of sources such as postmarketing data, literature, and clinical trial data. This review was supplemented by a review of AERS data conducted by the Office of Surveillance and Epidemiology (OSE)
4. Reckitt Benckiser's evaluation of issues related to the use of buprenorphine in pregnancy
5. Reckitt Benckiser's evaluation of information about accidental pediatric exposure, which was submitted to substantiate the public health importance of the individually-packaged strip product.

8.3 Brief Descriptions of Studies Included in Safety Review

The table below describes the studies included in the general safety review of this application. More detailed descriptions of each study included in the Clinical Review.

Study	Main Features	Enrollment	Comments
RB-US-07-001	12 week, open-label study in patients already stabilized on Suboxone; AEs and oral mucosal exams at clinic visits.	194	
RB-US-07-002	Inpatient, five days of buprenorphine treatment after a period of morphine stabilization. Compared Suboxone (b) (4) to buprenorphine strip; Labs, EKGs, mucosal exams, AEs.	49 enrolled; 38 treated with Suboxone strip or buprenorphine strip.	
Clinical Pharmacology Program (17 studies) (See Clinical Pharmacology review for full table of studies)	Crossover studies; Subjects under naltrexone blockade; Maximum exposure 3 doses	Subutex (N=206) Buprenorphine Soluble Film (N=351) Suboxone (N=266) Suboxone (b) (4) (N=412)	Only SAEs and AEs relevant to oral tolerability reviewed

Additionally, the post-marketing safety experience relevant to three specific safety issues (hepatic safety, use in pregnancy, and accidental pediatric exposure) were reviewed and are discussed below.

8.3.1 Study RB-US-07-001

Briefly, this study was designed to recruit patients "from the pool of patients being treated at the clinical site for opioid dependence who are on maintenance buprenorphine/naloxone sublingual tablets," and to randomize them to use the investigational product either sublingually or buccally for the next 12 weeks, during which AEs would be collected and oral mucosal exams performed at biweekly visits. Safety data from this study were evaluated with a focus on spontaneously-reported adverse events and findings of oral mucosal exams. Primary attention was given to the subset of patients assigned to use the study medication by the sublingual route, as the buccal route has not been proposed in the submitted labeling.

A total of 194 subjects from three study centers were screened and subsequently randomized to treatment with buprenorphine and naloxone soluble film via sublingual administration. (An additional 188 subjects were assigned to treatment by the buccal route. This group does not provide information relevant to the method of use claimed in this application and will generally not be discussed further.) Overall, 99% of the subjects were white, 64% of the subjects were male, and the average age was approximately 36 years (range 19-71 years), with over half of the participants in the 21-35 age group. At baseline, 99% had no oral mucosal abnormality.

Of 194 subjects randomized, 61% were considered "completers," defined as subjects who completed at least 84 days of buprenorphine and naloxone soluble film therapy, with a clinic visit not more than seven days after last soluble film administration. Most common reasons for discontinuation were loss to follow-up and withdrawal of consent. Information pertinent to adverse events leading to discontinuation was recorded in two different places; at Agency request, Reckitt Benckiser provided a tabulation using both sources of information that was used to create the (reviewer-constructed) subject disposition table below, which illustrates that adverse events were not frequently cited as the reason for study drug discontinuation.

Patient Disposition, RB-US-07-0001

	N	%
Randomized	194	
Treated (at least one dose)	194	100%
Completed all study visits	125	64%
Statistical Analysis Plan-defined completers[a]	118	61%
Recorded as "discontinued due to an adverse event" on study termination page (not in CRF)	5	3%
AE listed in CRF listed with action "study medication permanently discontinued"	4	2%
Withdrawn from study (CRF)	63	32%
Subject withdrew consent	12	6%
Investigator decision	10	5%
Sponsor decision	8	4%
Protocol violation	2	1%
Lost to follow-up	17	9%
Other	19	10%
incomplete termination data	1	1%

[a]Excludes major protocol violators

Extent of Exposure

The table below illustrates the cumulative exposure to the experimental product. This shows that there are 126 patients exposed for 12 weeks at any dose. Considering only those using the product in the labeled range (generally 12 mg-16 mg), there appear to be fewer than 80 patients contributing three months of safety data. It is known, however, that patients may also be maintained on lower doses, and considering patients on 8 mg/day or higher, the requested safety database of 100 patients was provided. However, few of the patients seem to have taken their medication as recommended in the labeling, as a single daily dose. Furthermore, although 12 mg/3 mg and 16 mg/4 mg strips were available for the clinical trial, they are not proposed for marketing. The currently-marketed product, Suboxone tablets, is available only in 2 mg/0.5 mg and 8 mg/2 mg formulations, so that patients taking the labeled dose of 16 mg/day are to use two tablets simultaneously, as was done in the clinical trial supporting approval of the tablet. In the film strip study, however, any patient using a single daily dose of 16 mg would have been provided with 16 mg strips, so there is likely to be essentially no data on using the film strip product as recommended in labeling, namely, two 8 mg strips sublingually used simultaneously.

Table 14.6.1.11 Cumulative Time on Dose by Dose Level in Study RB-US-07-0001
(Safety Set)

Treatment: Suboxone (b) (4) Sublingual (N=194)

	Number of weeks on dose											
Dose Buprenorphine/Naloxone(mg)	1	2	3	4	5	6	7	8	9	10	11	12
At least 2	179	176	176	164	164	158	158	152	152	141	139	126
At least 4	177	174	174	162	162	158	158	152	152	141	139	126
At least 6	168	165	165	153	153	149	149	143	143	131	128	118
At least 8	163	161	160	149	149	145	145	139	138	126	124	114
At least 10	118	117	117	107	104	100	98	93	93	85	83	77
At least 12	115	114	113	104	102	99	98	93	93	85	83	77
At least 16	109	108	107	100	99	96	95	90	90	82	80	74
At least 17	63	63	61	56	56	47	45	39	39	36	35	31
At least 18	62	62	61	56	56	47	45	39	39	36	35	31
At least 20	62	62	61	56	56	47	45	39	39	36	35	31
At least 24	61	61	60	56	56	47	45	39	39	36	35	31
At least 28	14	14	12	10	10	8	8	6	6	4	4	3
At least 32 or more	14	14	12	9	9	7	7	5	5	4	4	3

8.3.2 Study RB-US-07002

This was a 34-subject inpatient study intended to demonstrate that neither buprenorphine nor buprenorphine/naloxone soluble film formulation would precipitate an opioid withdrawal syndrome during initiation of treatment. Subjects were initially stabilized on morphine and then underwent challenge sessions with naloxone and placebo to ensure that subjects could detect opioid withdrawal. Subjects who met the criteria to continue in the study were randomized to treatment with buprenorphine soluble films or buprenorphine/naloxone films. Treatment with buprenorphine was initiated with several divided doses of 4 mg each (as is the recommended practice for office induction) totaling 12 mg the first day, with subsequent dosing of 16 mg-24 mg/day as a single daily dose for four additional days. Subjects were evaluated for the severity of withdrawal symptoms using physiological and behavioral measures. Safety measures included adverse events (AEs), oral mucosa exams, vital signs, electrocardiogram (ECG), and clinical laboratory measures (chemistry, hematology, and urinalysis).

Of 79 subjects screened, 49 were eligible and entered the morphine maintenance phase. Ten subjects were not randomized to treatment with buprenorphine or buprenorphine/naloxone films, either because they did not meet criteria for being able to detect withdrawal during the naloxone challenge session or for other reasons, and one subject who was randomized withdrew before receiving buprenorphine. Therefore, baseline data on 49 subjects and on-treatment data on 38 subjects (20 buprenorphine, 18 buprenorphine/naloxone) are available. Of these, 31 subjects (16 buprenorphine, 15 buprenorphine/naloxone) completed five days of treatment with the soluble films. These subjects do not change the extent of exposure tabulation given above because none were on study drug as long as one week.

The data from this study were included in the review of oral mucosal tolerability and clinical laboratory effects.

8.3.3 Clinical Pharmacology Program

The clinical pharmacology program was conducted in healthy volunteers under naltrexone blockade. Therefore, the overall safety findings from this program do not reflect the safety profile of buprenorphine as it is used in the target population, both because of the concomitant use of naltrexone, and because of the difference in tolerance to opioids. I did not review the overall adverse event profile but focused on local tolerability, and also reviewed the serious adverse events for any possibly relevant cases.

8.4 Safety Findings

Overall, no major new safety findings concerning the combination of buprenorphine and naloxone were identified in this review.

Almost all of the safety experience with the proposed new formulation was derived from a single study. This study had a number of flaws, including inadequate training of personnel conducting safety exams, inconsistent recording of findings, treatment of participants with dosing regimens not recommended in the proposed labeling, and a high drop-out rate. As a result, although no major safety concerns arose in this study, the quality of the data and their relevance to the proposed labeling are questionable.

8.4.1.1 Deaths

There were no deaths in the development program for this product.

8.4.1.2 Serious Adverse Events

8.4.1.2.1 Study RB-US-07-0001

Six SAEs were reported in Study RB-US-07-0001. Of these, several were clearly unrelated to study drug (all were assessed as unrelated by the sponsor). The table below briefly lists the events and my assessment of relatedness. Events from both the sublingual group and the buccal group are included in this presentation for completeness.

One of the events (patient 333149) is suggestive of precipitated withdrawal, and may therefore be related to the enhanced bioavailability of the naloxone component in the new formulation.

Patient	Event	Comment
Sublingual		
333010 35 yo F	Injuries sustained as a passenger in an MVA	Unrelated
333073 32 yo F	Cervical cancer dx after ~2 months on study drug	Unrelated
333233 31 yo M	Kidney stones in pt w/previous h/o kidney stones, dx after ~5 wks on study drug	Unrelated
333149 49 yo M	Nausea, chest pain, vasovagal syncope w/injury during initiation of study drug treatment at high dose	Possibly related
Buccal		
111011 37 yo M	MVA, no details, ~wk 5 of study drug	Cannot assess
111047 30 yo M	Esophageal cancer dx ~wk 6 of study drug	Unrelated

8.4.1.2.2 Study RB-US-07-0002

No SAEs were reported in this study.

8.4.1.2.3 Clinical Pharmacology Program

One serious adverse event occurred in the clinical pharmacology program, a case of optic neuritis during the third period of a crossover study with dosing separated by several weeks. Relationship to study drug cannot be determined.

8.4.2 Dropouts and/or Discontinuations

A total of 8 discontinuations due to adverse events (2% of participants) were identified in Study RB-US-07-001. Inspection of narratives suggests that only two of these were discontinued for drug-related adverse events, and in both cases the events are suggestive of withdrawal.

In Study RB-US-07-002, two subjects in each treatment arm discontinued during the first day of soluble film dosing. Only two of these were coded as discontinuing due to adverse events, but all four discontinued in similar circumstances, namely, withdrawal symptoms experienced during the first day of induction.

Because Reckitt Benckiser did not identify what treatment was administered associated with the discontinuation due to AE, noting that "Because of the crossover nature of the studies, summaries represent subjects according to the treatment of the first period of the study," it is not possible to determine whether any of the treatment arms (buprenorphine strips, Suboxone strips, Subutex tablets, Suboxone tablets) was more likely to lead to discontinuation due to adverse events. Overall, 2-3% of participants discontinued due to AEs. Inspection of the submitted narratives suggests that most patients who discontinued did so because of nausea and vomiting. These symptoms may be caused by naltrexone given prior to the test article.

8.4.3 Submission-Specific Primary Safety Concerns

8.4.3.1 Oral Mucosal Tolerability

Local mucosal effects of the strip formulation were identified as a key safety concern for this review and a potential way in which the new formulation might differ from the approved one. Notably, there are no AERS reports associated with Suboxone coded to HLGT Oral Soft Tissue Conditions.[5]

In summary, the main safety study conducted to address this concern identified no particular treatment-emergent safety issues related to the mouth, but data from both the clinical pharmacology program and a the small, inpatient, induction study suggest that the strip formulation may be associated with treatment-emergent oral complaints, although none would be considered serious. The data from the clinical pharmacology program suggest that the

[5] Search performed by Dr. Afrouz Nayernamaa 6/5/09

filmstrip formulation may be more irritating than the tablet. For a variety of reasons, the data from the large safety study (which identified almost no abnormalities) are not convincing. One potential complication in evaluating the oral mucosal tolerability of this product is the ambiguity of the dosing directions provided in the clinical studies.

In the clinical study, RB-US-07-0001, where subjects were self-administering the medication, the protocol indicated that "trained staff or the subject will place the film in the mid portion of the subject's *lateral sublingual space* (emphasis added); one film on each side (when more than one strip is needed) and if three strips are needed the third strip will be placed in the mouth at least five minutes after the other two to allow time for the first two strips to dissolve. The subjects will be told that films should NOT be chewed or swallowed. Subjects will be instructed not to swallow after dosing until the film is completely dissolved or after five minutes. The subjects will be told to hold the film in a stationary position and to place no more than 2 sublingual films *under the tongue* (emphasis added) at once.

In the clinical pharmacology studies, the protocols stipulated, e.g., "research staff will place the film sublingually (above the sublingual protuberance and across the frenulum, and within the confines of the sublingual fringes as much as possible)" or "research staff will place the films above the sublingual protuberance and across the frenulum, and within the confines of the sublingual fringes as much as possible. The first film strip (8 mg/2 mg) will be placed sublingually on the subject's right side. The second film strip (2 mg/0.5 mg) will then be placed sublingually next to the first film strip and the third film strip (2 mg/0.5 mg) will be placed next to the second film strip (on the opposite side from the first film strip). The film strips will be placed starting on the subject's right hand side moving across the sublingual space towards the subject's left hand side"

Although no one on the review team was able to discern that either of the sets of instructions given above meant that the strips were placed (b) (4), Reckitt Benckiser's representative reported that:

(b) (4)

(b) (4)

Protocol RB-US-07-0002 offered no specific instructions for dosing the film strips and therefore it is not clear whether these were placed (b) (4) variably based on the interpretation of the individual subject or study staff member.

At this time, it is not clear whether this difference has clinical significance. (b) (4) Both the Division of Dermatology and Dental Products and the Clinical Pharmacology team have been asked to comment on the potential clinical significance, but may require additional information from Reckitt Benckiser in order to make this assessment.

8.4.3.1.1 Oral Exams

Specific exams of oral mucosa were conducted only in Studies RB-US-07-001 and RB-US-07-002. In RB-US-07-0001, the study drug appears to have been placed on the floor of the mouth ("in the lateral sublingual space"). Placement is not described for RB-US-07-0002.

8.4.3.1.1.1 Study RB-US-07-0001

Study RB-US-07-001 was conducted primarily to identify any new safety concerns related to the delivery of the buprenorphine/naloxone combination in a new dosage form, a soluble filmstrip for transmucosal delivery. No products using this type of delivery system are marketed, although the technology is similar to the strips used for oral delivery of cough/cold products and breath fresheners. These are placed on the dorsal surface of the tongue and not in the less keratinized sublingual area. Special attention was given to evidence of local oral irritation.

Oral exams were conducted at each visit, albeit not by dental professionals or others specifically qualified to evaluate the oral mucosa. It is likely that only the most obvious and dramatic of oral mucosal abnormalities would have been detected in this way. The protocol stipulated that any abnormal findings were to be recorded both as an oral exam score but also as an adverse event; however, this appears to have been done inconsistently.

Overall, 10 of the 194 subjects randomized to treatment with sublingual study drug had either a treatment-emergent abnormal exam recorded, or a spontaneous adverse event referable to the mouth/tongue/oral mucosa. No patient had both.

According to Reckitt Benckiser, 121 subjects completed an oral mucosa exam at visit 10 and at all previous visits. (Because Visits 1 and 2 were combined at one study site, this represented

9 mucosal exams many subjects.) Review of the submitted datasets located 9 or 10 exam results for 120 (not 121) subjects.

The overwhelming majority of the oral exams were graded as "0" (normal mucosa).
Only 6 study participants treated with sublingual study drug had an abnormal exam at any time during the study. One additional patient (333073) has an adverse event of "oral mucosal exam=grade 1 abnormality" recorded in the AE dataset but no abnormal exam recorded in the Oral Exam dataset.

In summary, these exams provided little evidence of treatment-emergent mucosal abnormalities, but may have lacked sensitivity due to the lack of training of the examiners. Furthermore, as will be discussed below, the dosing regimen employed by the vast majority of subjects differs substantially from the recommended dosing regimen in the label. Specifically, almost no patients were using a single daily dose of study drug; therefore the data represent findings collected in the setting of patients using small, divided doses rather than the specific doses in labeling. Indeed, because a 16 mg strip was provided for the study but is not proposed for marketing, it is unlikely that any patient would have been treated with two 8 mg strips simultaneously, as recommended in the labeling as the target dose for all patients. (b) (4)

[redacted]

8.4.3.1.1.2 Study RB-US-07-0002

In this study, an oral mucosal examination was performed at baseline and at discharge from the residential unit to determine if the soluble film caused any irritation of the mucosa. Baseline abnormalities (localized mucosal erythema and/or irritation without ulceration, assessed as Grade 1 severity) were common at baseline. Seven of the 38 study participants who were randomized to treatment (18%) had abnormalities at baseline. In addition, of the fifteen subjects listed as "not treated" (subjects discontinued during morphine stabilization phase prior to administration of film strip), six (40%) had baseline Grade 1 abnormalities. This is an overall rate of baseline abnormalities in 25% of those admitted to the research unit, in contrast to the very low rate of abnormalities observed in study RB-US-07-0001.

After four days of film strip treatment, four subjects, one in each arm, had abnormalities at discharge which were not present at baseline, including one subject described as having developed "blisters on gums" on the last day of buprenorphine film strip administration. The Ns in the table below represent the patients in the sponsor's "evaluable" population.

	Buprenorphine strips N = 19	Buprenorphine/naloxone strips N = 16
Treatment-emergent mucosal abnormalities	2 (11%)	2 (13%)

It is notable that the rate of both baseline and treatment-emergent mucosal abnormalities was much higher in this carefully-monitored population than in the population that participated in the safety study. Note that the duration of treatment with the film strip products in this study was only four days. The specific method of administration is not described in the protocol.

The more careful monitoring in this study identified a much higher rate of mucosal abnormalities, both at baseline and emerging during treatment. This further underscores the concern that the main safety trial lacked sensitivity to identify local oral effects of the study drug.

The protocol for this study did not give specific instructions about placement of the film strips and therefore it is not known how they were administered.

8.4.3.1.2 Adverse Events Related to the Mouth

8.4.3.1.2.1 Study RB-US-07-0001

A string search in the verbatim term field and the MedDRA LLT field for "mouth," "oral," "gum," "ging," "gloss," "oral," and "tongue" was used to supplement the HLGT "Oral Soft Tissue Conditions." Using this method, nine patients reporting events referable to the mouth, tongue, and oral mucosa were identified. These included three patients for whom the AE was an oral exam abnormality and six for whom the AE was a spontaneously-reported AE. Notably, there were no spontaneous complaints from the three subjects with oral mucosal abnormalities on exam. In addition, there were two patients for whom oral mucosal exam abnormalities were recorded in the Oral Exam database who were not listed in the AE dataset. Notably, these two patients also had no spontaneously-reported oral complaints.

Complaints reported spontaneously included:

Preferred Term	# of Patients
GLOSSODYNIA (includes verbatim terms burning of tongue, burning tip of tongue, tongue tender)	3
HYPOAESTHESIA ORAL (includes verbatim term numbness tongue)	2
TONGUE COATED	1

In this study, directions called for the study drug to be placed in the "lateral sublingual space" and "under the tongue." Therefore, it seems unlikely that the product was used as recommended in the proposed labeling (i.e., (b) (4)

8.4.3.1.2.2 Study RB-US-07-0002

Only one adverse event referable to the oral mucosa was reported; this was the above-mentioned patient with gingival blisters. The method of study drug administration in this study is not known.

8.4.3.1.2.3 Clinical Pharmacology Program

Reckitt Benckiser identified the following adverse events related to the oral mucosa in the clinical pharmacology program. The Ns represent the number of subjects participating in that arm of the study. Most studies had crossover design and subjects could have received more than one treatment. Events were grouped according to the treatment period in which they occurred[6]. Not enough information is provided to determine whether the cases coded as "herpes" were actually viral eruptions vs. some other time of mouth sore that could potentially be drug-related. (One case had lower level term of "cold sore.") However, even with these events excluded it appears that the strip formulations are more likely than the tablet formulations to be associated with complaints referable to the mouth. This population also, obviously, reported far more oral adverse events than did the participants in Study RB-US-07-0001. In these studies, the protocol called for the study drug to be placed "above the sublingual protuberance and across the frenulum, and within the confines of the sublingual fringes as much as possible." Although it is not entirely clear what is meant by this, Reckitt Benckiser has indicated that the strips were to be placed (b) (4) . This may or may not have been completely understood by the site investigators.

"Special Interest" Adverse Events in Clinical Pharmacology Program

	Subutex		Buprenorphine Soluble Film (N=351)		Suboxone		Suboxone (b) (4)	
Preferred Term	(N=206)				(N=313)		(N=459)	
At Least One Special Interest Adverse Event	2	1%	13	4%	8	3%	31	7%
PARAESTHESIA ORAL	1	0.5%	7	2%	2	1%	6	1%
DYSGEUSIA	1	0.5%	1	0.3%	3	1%	4	1%
TOOTHACHE	0		2	1%	2	1%	1	0.2%
ORAL HERPES	0		0		0		4	1%
HYPOAESTHESIA ORAL	0		1	0.3%	0		2	0.4%
SALIVARY HYPERSECRETION	0		0		0		2	0.4%
APHTHOUS STOMATITIS	0		0		1	0.3%	0	
CHEILITIS	0		0		0		1	0.2%
GINGIVITIS	0		0		0		1	0.2%
ORAL PAIN	0		1	0.3%	0		0	
SALIVA ALTERED	0		1	0.3%	0		0	

Table adapted from Table 14.7.14.1 in 4-month Safety Update

These data again cast doubt on the seemingly reassuring findings of the main safety study.

[6] The CRF did not have this information, and it had to be calculated by Reckitt Benckiser based on the date of the event.

8.4.3.2 Precipitation of Withdrawal

Patients dependent on full agonists may experience withdrawal when buprenorphine treatment is initiated because of the relative reduction in receptor activity due to buprenorphine's partial agonist properties. This is more common in patients on long-acting agonists such as methadone, and is mitigated by initiating treatment when patients are already exhibiting signs and symptoms of withdrawal, indicating less than full receptor occupancy.

However, even patients in some degree of withdrawal can experience abrupt withdrawal precipitation in response to naloxone. Although naloxone is not well-absorbed sublingually, it is absorbed to some degree and data submitted in the NDA for Suboxone suggested that initiation of treatment with Suboxone was more likely to precipitate withdrawal than treatment with Subutex. For this reason, the Division raised concerns about the possibility of precipitation of withdrawal due to the greater bioavailability of naloxone in the film strip product

As noted above in discussion of discontinuations due to adverse events, two participants in Study RB-US-07-0001 and four participants in Study RB-US-07-0002 discontinued prematurely in association with symptoms consistent with withdrawal. Although the patients in RB-US-07-0002 were in acute withdrawal due to the design of the study, and may have been experiencing inadequate treatment of withdrawal (i.e., lack of efficacy, rather than and adverse effect of the drug), in theory, the participants in RB-US-07-0001 should have been stabilized patients, not using illicit drugs, and having no reason to experience withdrawal symptoms. In addition, one patient in RB-US-07-0001 who ultimately went on to complete the study had AEs of nausea and vomiting shortly after treatment initiation, which could be attributed to withdrawal.

Study RB-US-07-0002 was intended to demonstrate a lack of precipitation of withdrawal by Suboxone strip, but the design was unsuitable to address our concerns. Division expressed the opinion that the most important question was whether any differential naloxone level would translate into decreased likelihood of a patient completing induction and becoming successfully stabilized on a dose of buprenorphine/naloxone. The study instead focused on group mean measures of withdrawal on the Clinical Opiate Withdrawal Scale (COWS).

However, the data submitted from this study do provide some insight into the experience of patients transitioning from a full agonist (morphine) to (b) (4) the buprenorphine/naloxone combination strip. The results were inspected but not reviewed in detail.

Briefly, subjects were stabilized on morphine and underwent a naloxone challenge to establish their ability to detect naloxone-precipitated withdrawal. Eligible subjects were randomized to treatment with 5 days of buprenorphine soluble films or buprenorphine/naloxone soluble films. The first day of dosing, participants received 4 mg buprenorphine (or 4 mg buprenorphine/1 mg naloxone) at 0900, 1100, and 2000 hours. (The use of 4 mg doses repeatedly as needed during the first day of dosing is a commonly-used, although not labeled, induction procedure.) Thereafter, dosing was titrated from 12 mg, once per day at approximately 0900 hours to 16-

24 mg/day as a single daily dose. Prior to and after each day's soluble films administration, subjects were evaluated for the severity of withdrawal symptoms.

Two subjects in each treatment arm discontinued during the first day of soluble film dosing. Because buprenorphine is to be initiated when patients are already in some degree of withdrawal, the experience of withdrawal is to be expected. Data included in the final study report indicate that, for two of the patients, withdrawal scores were slightly higher one hour after study drug administration than prior to administration, and for one, the score was unchanged. (Scores are expected to decline when buprenorphine is administered to a patient already in withdrawal).

The following are my conclusions regarding this study:
1. The design is not optimal for answering questions about the impact of the differences between the new and old formulations.
    - Inpatients stabilized on morphine may not be representative of patients coming into treatment
    - The comparison was between induction with buprenorphine/naloxone strips and induction with buprenorphine-only strips (rather than strips vs. tablets)
    - The analysis based on group mean withdrawal scores
        - Patients who dropped out after 1-2 doses of drug during first induction day were excluded from the group analysis.
            - This would exclude any patients with precipitated withdrawal, which occurs at the beginning of dosing.
        - The study not show whether patients on new product are as likely to be able to make the transition from street drugs to a stable dose of buprenorphine as patients on the approved product
2. However, the results were generally not concerning.
    - Two patients in each arm dropped out on first buprenorphine dosing day
    - One *in each arm* had withdrawal scores that were higher after dosing than before (note that all patients are in withdrawal before dosing; this is usual clinical practice intended to prevent precipitation of withdrawal by buprenorphine).
    - The others had lower scores or no change.
    - This scenario more consistent with patients dropping out due to lack of efficacy (i.e. insufficient relief of withdrawal) than due to precipitated withdrawal.
    - COWS scores decreased after dosing for almost all participants. About 60% in each arm had scores that decreased to the mild range after dosing.

8.4.3.3 Accidental Pediatric Exposure

Dr. Elizabeth Kilgore conducted a review of the information relevant to this safety issue, as well as hepatic safety and the use of buprenorphine in pregnancy. See her review for additional detail. In her review, she considered Poison Control Center data and literature reports, and concluded that accidental pediatric exposure is a significant and growing issue with Suboxone and Subutex tablets. The same issue can be expected with the proposed product. No cases with fatal outcome have been reported, but some involved life-threatening and potentially fatal reactions. The individual child-resistant pouches for the new product are a helpful step, but the more rapid dissolution of the new formulation and the difficulty in removing the soluble film once it is placed in the mouth has the potential to produce more severe outcomes if small children gain access to the soluble strip product. The labeling should emphasize the risk of pediatric exposure and the need to keep the product away from children. One element of the REMS should also address this risk, using a MedGuide to communicate with patients about medication safety in the home. In addition, based on the literature review, the Overdose section of the physician labeling should advise that naloxone may be useful in overdose cases.

8.4.3.3.1 Frequency of Accidental Pediatric Exposure

The table below was constructed by the review team using data provided by Reckitt Benckiser via a contract with the (b) (4) to provide specific information about pediatric exposures to buprenorphine products, combined by the review team with distribution data provided by OSE to show the number of reports of accidental exposure per million prescriptions dispensed.

(b) (4) **Toxic Exposure Surveillance System Annual Reports All Buprenorphine**

Age	Year	Number Cases	Prescriptions Dispensed[1]	Comments
All aged children	2004	59	(b) (4)	
< 6 yo	2006	192		
< 6 yo	2007	412		
< 6 yo	2008[2]	589		

(b) (4) data from OSE review
from Q1-3 only; sales from Q1-4

In order to place this data into some context in comparison to accidental pediatric exposures to other opioids, the review team constructed the table below.

Poison Control Center Reports in Children under Age 6, 2007

Substance	PCC[a,b] reports	Million Rxs[c]	Reports per Million Rx
Buprenorphine (all)	419	(b) (4)	
Subutex	13		
Suboxone	399		
Codeine	280		
Meperidine	43		
Methadone	318		
Morphine	264		
Oxycodone	525		
Pentazocine	8		
Propoxyphene	27		
Tramadol	709		

[a] Mentions of specific drugs in cases involving patients under age 6 from 2007 (b) (4) report
[b] Mentions of buprenorphine products from Reckitt Benckiser's 7/3/08 report of their post-marketing surveillance program for Suboxone and Subutex.
[c] Distribution data from a consult prepared recently by the Drug Use Data Analysis team in OSE for the Division of Oncology.
[d] Note that methadone dispensed via opioid treatment programs is not included in this total; therefore distribution is underestimated and the reporting rate is overestimated.

This analysis, comparing numbers of reports to numbers of prescriptions, is one of many imperfect ways of attempting to correct numbers of reports for extent of distribution, but it does allow some sense of context and illustrates that the number of accidental exposures of small children to buprenorphine is very high, considering the extent of distribution.

8.4.3.3.2 Consequences of Accidental Pediatric Exposure

Dr. Kilgore reviewed literature submitted by the Applicant that provided information on the consequences of accidental pediatric exposures. She observed the following:

- The number of pediatric accidental exposure cases has increased from 192 in 2006 to 589 in 2008, commensurate with the increase in distribution of buprenorphine products.
- Most patients had minor or moderate adverse events reported; no fatal cases were reported.
- The majority of cases involve children under 6.
- Where comparisons to methadone were available, methadone cases appeared to have more severe outcomes than buprenorphine cases.
- The most common adverse events reported were somnolence, emesis, and miosis.
- Treatment included naloxone, i.v. fluids, activated charcoal, oxygen and ipecac. A response to naloxone was reported, although high (and repeated) dosing was needed.
- More severe cases required repeated naloxone and some cases required respiratory support.

Some authors observed that children may be inclined to suck on or chew tablets, rather than swallow them whole, which promotes buccal absorption. Because of buprenorphine's poor

oral bioavailability, tablets swallowed whole would be less harmful. It should be noted that the proposed filmstrip product cannot be spit out easily and dissolves quickly. Therefore, to the extent that some cases may be mitigated by the child spitting out the tablet before full absorption, the filmstrip product could be more hazardous than the tablet. However, the unit-dose packaging will help protect against this as long as the medication is not removed from the packaging and left out. (This may occur if patients use fractions of a strip, which is apparently common practice with tablets.)

Reports of response to naloxone in pediatric exposure cases are relevant, because the current labeling does not provide guidance on the use of naloxone in overdose. Labeling should be revised to reflect the advice that naloxone, at higher-than-usual doses, and potentially repeated doses, may be useful in overdose.

8.4.3.4 Hepatic Safety

The potential hepatotoxicity has been a topic of concern for some time, and was identified as a deficiency in the 1/26/01 Approvable action on the NDAs for Subutex and Suboxone. After careful review of the available information, it was observed that the there was a high frequency (12.3%) of clinically abnormal LFTs in the clinical trials, and a broad spectrum of hepatic adverse events in the post-marketing safety database, including severe cases of hepatic disease. Interpretation of hepatic adverse events and LFT data from each of these data sources has been limited by the presence of confounding factors, such as abnormal LFTs at baseline, ongoing intravenous drug abuse, chronic hepatitis B or C infection, concurrent alcohol use, use of potentially hepatotoxic concomitant medications, and other factors. Nonetheless, there are cases in both the clinical trials database and in the post-marketing database suggesting that buprenorphine may have a causative or contributory role in the development of hepatic abnormalities. No firm conclusion, however, could be made about these cases, mainly because of insufficient detail. Appropriate warnings were included in the label, and a post-marketing study to define the role of buprenorphine in the development of hepatic abnormalities in opiate addicts was included as a post-marketing commitment. This study, being conducted by the National Institute on Drug Abuse, rather than by Reckitt Benckiser, has been slow to enroll and no results shedding light on hepatic safety are available.

As part of this submission, Reckitt Benckiser was asked to do a comprehensive update on the question of hepatic safety, using any sources of available information. Dr. Elizabeth Kilgore reviewed the submitted information. In addition, Dr. James Kaiser of OSE reviewed the AERS database to determine whether any additional information was available through these reports that could inform labeling or future studies.

8.4.3.4.1 Laboratory Data

One literature report with some detail on pre- and post-treatment laboratory values[7] was submitted, along with several other publications not providing much relevant information. In this report, the authors included information in the text that was used to construct the table

[7] Lofwall et al, Addict Disorder Therapeutic Treatment 2005; 4:49-64.

below, comparing shifts between abnormal and normal LFTs in patients treated for 16 weeks with either buprenorphine or methadone.

Percent of Subjects with Change in Abnormal Liver Function Tests

LFT Analyte	# Subjects Change in LFT Normal to Abnormal		# Subjects Change in LFT Abnormal to Normal	
	Buprenorphine	Methadone	Buprenorphine	Methadone
SGOT	19/48 (39.6%)	11/42 (26.2%)	2/7 (28.6%)	5/11 (45.5%)
SGPT	17/43 (39.5%)	11/40 (27.5%)	4/13 (30.8%)	3/12 (25.0%)

(Source: Table prepared by Dr. Kilgore from text of Lofwall article referenced above)

This study demonstrates that fluctuations between normal and abnormal are quite common in this population, but suggests that buprenorphine-treated patients may be more likely to develop new abnormalities and less likely to have existing abnormalities normalize than patients treated with methadone.

Dr. Kilgore also analyzed the data from Study RB-US-07-0002, in which all subjects were stabilized on morphine for several days, and those who were eligible to continue were randomized to either Suboxone strip or buprenorphine strip for five days. Baseline and end-of-study LFTs were obtained on most subjects. In this data, the 10 subjects who were not randomized to treatment with either buprenorphine product provide a control group. Patients with increases of at least 10% from baseline, regardless of whether the baseline value was normal or abnormal, were included in the tabulations below.

Subjects with Treatment-emergent elevations in hepatic enzymes, Study RB-US-07-002

	Group A (Buprenorphine)		**Group B (Suboxone)**		**Untreated (Morphine only)**	
Analyte	**N=18**	**(%)**	**N=16**	**(%)**	**N=10**	**(%)**
ALT + AST	4	(22)	2	(12)	2	(20)
ALT	2	(11)	1	(6)	-	
AST	-		-		-	
AP	2	(11)	-		1	(10)
ALT +AST+ AP	-		1	(6)	-	
AST + AP	-		-		-	
Total	8	(44)	4	(25)	3	(30)

AP = alkaline phosphatase
(Source: Table prepared by Dr. Kilgore from data provided by Applicant's Study Report)

The results were further categorized according to whether hepatic enzymes worsened from a normal baseline or worsened from an already elevated baseline.

Type of Hepatic Change Experienced by Subjects, Study RB-US-07-002

	Group A (Buprenorphine)		**Group B (Suboxone)**		**Untreated (Morphine only)**	
ALT	**N=18**	**(%)**	**N=16**	**(%)**	**N=10**	**(%)**
Any worsening	6	(33)	4	(25)	2	(20)
Normal to abnormal	5	(28)	3	(19)	1	(10)
Abnormal to worsened	1	(5)	1	(6)	1	(10)
AST						
Any worsening	4	(22)	3	(19)	2	(20)
Normal to abnormal	2	(11)	1	(6)	1	(10)
Abnormal to worsened	2	(11)	2	(13)	1	
AP						
Any worsening	2	(11)	1	(6)	1	(10)
Normal to abnormal	1	(6)	1	(6)	-	
Abnormal to worsened	1	(6)	-		1	(10)

(Source: Table prepared by Dr. Kilgore from data provided by Applicant's Study Report)

These data show that hepatic enzyme fluctuations are extremely common in this population. Although the findings suggest that those treated with buprenorphine strip were more likely than those not treated with buprenorphine to develop abnormalities, the lack of a similar finding in the Suboxone (buprenorphine/naloxone) strip group is difficult to explain.

Most elevations were regarded as not clinically significant. The two cases with "clinically significant" changes did occur in patients treated with Suboxone strip. Both of these cases occurred in patients who were described as having a "reported" or "possible" history of viral hepatitis (serology does not seem to have been documented).

These data highlight the difficulty in interpreting hepatic data in this population.

8.4.3.4.2 Hepatic Adverse Events

Dr. Kilgore reviewed the hepatic adverse events from the Suboxone Strip database and the postmarketing events submitted by the Applicant. Dr. James Kaiser reviewed hepatic adverse events in the AERS Database.

One subject in the Phase 1 program experienced an AE of "liver enzyme elevation" discovered in routine discharge visit labs on (b) (6) after being discontinued for failure to keep the appointment for the third period of the study. Values included ALT 107 U/L (screening was 14 U/L), AST 309 U/L (screening value 19 U/L), LDH 542 U/L (screening 197 U/L), and total bili 0.3 mg/dL. She had received a single dose of buprenorphine/naloxone film (12 mg/3 mg) on August 5th, and a single dose of Suboxone tablets on August 19th. Each of these was accompanied by three days of dosing with naltrexone. Repeat labs two days later showed declining, but still abnormal values. No further follow-up was reported. Because naltrexone is also associated with hepatic enzyme elevation, it is difficult to determine the relationship to buprenorphine.
In the RB-US-07-0002, there was one case of hepatic enzyme elevations reported as an AE.

No hepatic-related AEs were reported in RB-US-07-0001.

Reckitt Benckiser's submission of post-marketing cases comprised 227 cases. Clinically asymptomatic LFT increase was the most frequently occurring AE (32%) followed by acute hepatitis (23%).

Narratives were provided for 18 hepatic SAEs and 10 deaths. Most cases were confounded or provided insufficient information to determine causality, but some cases occurring in patients being treated with buprenorphine for pain (rather than drug addiction) suggest that not all hepatic events can be dismissed as attributable to the other risk factors seen in the addict population. Cases with resolution on dechallenge also further suggest a causative role of buprenorphine. Although none could be clearly attributed to buprenorphine, hepatic AEs with fatal outcome have been reported and are not currently described in labeling.

Both reviewers concluded that the current labeling should be slightly revised to reflect the existence of reports outside the population being treated for drug dependence, and the reports of fatal cases and cases with positive dechallenge.

In addition, I recommend the post-marketing commitment to study the comparative effects of buprenorphine and methadone on the liver should be reiterated at this time as a post-marketing requirement.

8.4.3.5 Study Drug Accountability/Diversion

Reckitt Benckiser has implied that this product may represent an advantage over the current tablet products with respect to diversion. Study drug accountability in Study RB-US-07-0001 was reviewed for information pertaining to this issue.

A search of the protocol deviation dataset using terms such as *lost, stolen, packet, strips, failed, return, missing* yielded several hundred listings which were inspected to remove events unrelated to study drug accountability. This yielded 294 events reported in 155 different patients (all at site 333, where total enrollment was 233) in which empty packets were not returned, unused study drug was not returned as required, or study drug was reported lost, stolen, or destroyed. About half of the patients had one such report but two or three reports by the same patient were common, and 6 patients had as many as 6-7 such violations. No action appears to have been taken by the study site.

Only Site 333 reported these events as protocol deviations. At Agency request, Reckitt Benckiser provided (in line listing form only, not a dataset amenable to analysis) a listing of patients with similar deviations at the other two sites. This revealed 18 (of 27 enrolled) patients at Site 777 with "missing" study drug supply (none "lost" or "stolen") and 118 (of 122 enrolled) patients at Site 111 with missing, stolen, or lost drug supply. Most of these patients are listed as having "missing" packets on only a single occasion; however, some are missing substantial quantities of packets (up to 377 packets at one visit), and some patients reported "stolen" or "lost" unused drug supplies on more than a single occasion.

At Agency request, Reckitt Benckiser provided a tabulation showing how many strips of each dosage strength were "prescribed" to patients (i.e., the amount the patient was instructed to use), how many were "dispensed" (patients were to get either a one- or two-week supply of medication, plus an additional three-day supply) and how many strips were returned, calculating the number of strips which were unaccounted for. In this tabulation, if a patient were dispensed medication and he/she did not return to the clinic prior to Visit 9 (or at all), the amount prescribed was considered to be zero, which elevates the calculation of the amount of drug considered to be "missing." Overall, 12,900 strips were provided to participants in excess of the amount prescribed. Of these, 5918 (46%) were not returned. Across sites the amount of missing study drug ranged from 38% of the strips due to be returned at Site 333 to 90% of the strips due to be returned at Site 777. The table below, constructed by the reviewer from the data submitted, illustrates the substantial quantity of drug supply unaccounted for.

Site	Dose	# of (b) (4) Dispensed	# of (b) (4) Prescribed	# of (b) (4) Returned	# of (b) (4) Expected to be Returned	# of (b) (4) Missing	% of Expected Returns Not Returned
111	2 mg	8,674	6753	1162	1,921	759	40%
	8 mg	6862	5411	773	1,451	678	47%
	12 mg	173	97	35	76	41	54%
	16 mg	207	155	33	52	19	37%
	total	15,916	12,416	2,003	3,500	1,497	43%
333	2 mg	3020	2412	459	608	149	25%
	8 mg	13687	10621	2053	3,066	1,013	33%
	12 mg	11490	9283	1221	2,207	986	45%
	16 mg	8917	7086	1080	1,831	751	41%
	total	37114	29402	4813	7712	2899	38%
777	2 mg	3213	2513	86	700	614	88%
	8 mg	4210	3338	59	872	813	93%
	12 mg	146	112	0	34	34	100%
	16 mg	448	366	21	82	61	74%
	total	8017	6329	166	1688	1522	90%
All	2 mg	14,907	11,678	1,707	3,229	1,522	47%
	8 mg	24,759	19,370	2,885	5,389	2,504	46%
	12 mg	11,809	9,492	1,256	2,317	1,061	46%
	16 mg	9,572	7,607	1,134	1,965	831	42%
	total	61,047	48,147	6,982	12,900	5,918	46%

No information on accountability of drug supply for the tablet formulation is available, because the registration studies were done under supervised administration conditions (and in some cases used a liquid formulation). Therefore, there is no basis for comparison but there does not appear to be any reason to conclude that this formulation rendered the study drug particularly resistant to diversion.

8.4.3.6 Use in Pregnancy

Current labeling identifies Suboxone and Subutex as Pregnancy Category C, and includes the CFR-mandated statement "There are no adequate and well-controlled studies of SUBOXONE or SUBUTEX in pregnant women. SUBOXONE or SUBUTEX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus." The label describes non-clinical findings of increases in neonatal mortality in rat studies with no safety margin.

Nevertheless, since the introduction of Subutex treatment of opioids dependence in France, some researchers have advocated the use of buprenorphine in pregnancy. Reckitt Benckiser also submitted a section addressing use of Suboxone and Subutex in pregnancy, but did not propose any changes to the labeling to promote its use.

Dr. Kilgore reviewed the submitted information. Literature reports included case series, small randomized studies (comparison to methadone), and studies using health care databases in European countries. Some studies suggested a lower incidence and severity of neonatal abstinence in infants of buprenorphine-treated mothers compared to infants of methadone-treated mothers. However, the results were equivocal and did not clearly demonstrate a benefit of buprenorphine, particularly in cases where patients continued to use illicit drugs, which, in some studies, was more likely with buprenorphine than with methadone.

Reports of adverse events in neonates and literature reports of neonatal outcomes were also submitted. Dr. Kilgore noted that the current language describing neonatal withdrawal in infants exposed to buprenorphine *in utero* did not fully capture the range of symptoms observed. Currently, the labeling describes "one case" of apnea, respiratory depression and bradycardia. Other cases of this nature have been reported and the label should be revised to delete the reference to a single case.

8.4.3.7 Common Adverse Events

The clinical pharmacology program was conducted in subjects under naltrexone blockade and Study RB-US-07-0002 involved only five days of dosing with the experimental drug; therefore only Study RB-US-07-0001 was analyzed for common adverse events.

Adverse events reported in Study RB-US-07-001 were collected by spontaneous report at study visits and coded using MedDRA. However, to facilitate comparison to the existing safety experience with the approved sublingual tablets, the MedDRA terms were mapped to corresponding COSTART terms. The tables below illustrate the COSTART-coded common adverse events in Study RB-US-07-001. Compared to the pivotal studies included in the approved labeling for Suboxone and Subutex, there was a substantially lower rate of adverse events reported. This may relate to the difference in population (stabilized at least 30 days vs. new entrants to treatment) or may reflect the overall cavalier conduct of Study RB-US-07-001.

Adverse Events reported in at least 2% of participants, by COSTART Body System and Preferred Term in Study RB-US-07-001

Body System/Adverse Event (COSTART Terminology)	Sublingual N=194 n (%)	Buccal N=188 n (%)	Total N=382 n (%)
At least one adverse event	54 (27.8%)	62 (33.0%)	116 (30.4%)
Body as a Whole	29 (14.9%)	34 (18.1%)	63 (16.5%)
Pain	8 (4.1%)	7 (3.7%)	15 (3.9%)
Accidental injury	5 (2.6%)	9 (4.8%)	14 (3.7%)
Infection	6 (3.1%)	7 (3.7%)	13 (3.4%)
Headache	2 (1.0%)	4 (2.1%)	6 (1.6%)
Skin and Appendages	7 (3.6%)	6 (3.2%)	13 (3.4%)
Rash	2 (1.0%)	6 (3.2%)	8 (2.1%)
Respiratory System	6 (3.1%)	5 (2.7%)	11 (2.9%)
Sinusitis	3 (1.5%)	4 (2.1%)	7 (1.8%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.
Data derived from: Clinical Study Report for RB-US-07-0001, Statistical Table 13.1.2.

Reckitt Benckiser proposes to include a (b) (4)

(b) (4)

The film strip can be expected to be associated with systemic adverse events similar to those seen with other formulations, and, if anything, may be more irritating locally.

8.4.4 Laboratory Findings

Clinical laboratory were not collected in Study RB-US-07-0001. Study RB-US-07-0002 included laboratory assessments at admission and discharge (a maximum of 5 days of exposure to buprenorphine). Hepatic enzymes increased during the brief period of treatment in this study. Other analytes did not show notable changes from baseline.

See discussion, above, of hepatic safety for a description of hepatic enzyme data.

8.4.5 Vital Signs

Vital signs were not collected in Study RB-US-07-0001. Vital sign data from RB-US-07-0002 reflects patients in acute withdrawal and provides little meaningful information.

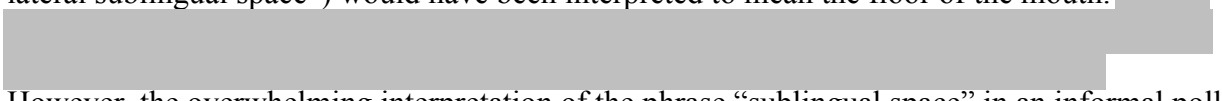
8.4.6 Electrocardiograms (ECGs)

No new ECG data was reviewed.

8.5 Safety Conclusions

8.5.1 Overall safety profile

The study conducted to gather overall safety data pertinent to this new formulation did not provide any indication that the adverse event profile of buprenorphine/naloxone film strips would differ from that of the Suboxone tablet. However, the study lacked sensitivity to identify new concerns. Furthermore, there may have been differences in the placement of the study drug between studies due to the ambiguous wording of the instructions in the protocol. It seems likely that the instructions given in the main safety study (to place the product "in the lateral sublingual space") would have been interpreted to mean the floor of the mouth. (b) (4)



However, the overwhelming interpretation of the phrase "sublingual space" in an informal poll of DAARP staff was "floor of the mouth," suggesting that study participants may well have been forcing film strips into the floor of the mouth beneath the tongue, potentially folding or bending the strips to make them fit. What impact this could have on either local tolerability or on pharmacokinetics is not known. A formal opinion from the Division of Dermatology and Dental Products will be requested but is not available at this writing.

8.5.2 Oral mucosal effects

Although the main safety study did not identify concerns related to oral tolerability, treatment-emergent mucosal abnormalities occurred within 5 days of treatment in 13% of participants in Study RB-007-0002, wherein monitoring was more thorough. Taken together with the 7% of clinical pharmacology study participants who reported adverse events involving the mouth when treated with buprenorphine/naloxone strips (as compared 3% treated with Suboxone tablets), it appears that buprenorphine/naloxone strips have the potential to cause local irritation in a substantial number of patients. The possibility that the product was applied differently in different studies may have contributed to the variability in results.

8.5.3 Hepatic effects

Hepatic effects, sometimes serious, have long been known to occur in patients treated with buprenorphine, but because of the nature of the population (viral hepatitis, concomitant use of other drugs and alcohol, etc), these cases have frequently been dismissed as probably unrelated to buprenorphine. Post-marketing cases in pain patients, cases with positive de-challenge, and cases without obvious alternative explanations provide growing support to the possibility that buprenorphine may play a role in hepatic injury. Reckitt Benckiser should further evaluate this in the ongoing post-marketing study, which should be reiterated as a post-marketing requirement.

8.5.4 Accidental Pediatric Exposure

No cases of accidental pediatric exposure were reported in the studies in this NDA. The unit of use packaging is intended to prevent accidental pediatric exposure by making the product less accessible, and to limit the administration, when it occurs, to a single dose. No data was submitted on the child-resistance of the packaging, but unit dosing does offer a way to limit exposure to one dose at a time. It should be noted, however, that the more rapid dissolution of the soluble strip formulation may be a relative disadvantage in allowing more drug to be absorbed before the child spits out the product. Furthermore, in a survey conducted by Reckitt Benckiser, many subjects reported using fractions of tablets. Fractions of film strips removed from the child-resistant pouch (not even contained within a prescription bottle, as a fraction of a tablet might be) would represent a hazard to children in the household. Efforts to communicate the need to prevent accidental pediatric exposure, e.g. via a Med Guide, should be a part of the Risk Evaluation and Mitigation Strategy.

8.5.5 Potential for Abuse, Misuse, and Diversion

(b) (4)

9 Advisory Committee Meeting

No Advisory Committee meeting was held pertaining to this application, because this product is a fairly straightforward line extension of an approved product.

10 Pediatrics

The active moiety of buprenorphine (with or without naloxone) has, and will retain, orphan designation for the treatment of opioid addiction. The sponsor's new formulation of buprenorphine falls under this designation and thus, pursuant to 21 U.S.C. 355c(g), is exempt from the pediatric study requirements under PREA.

Reckitt Benckiser has indicated that they have no firm plans for conducting pediatric studies, (b) (4)

11 Other Relevant Regulatory Issues

11.1 DSI Audits

The Division of Scientific Investigation (DSI) was asked to inspect all three sites of Study RB-07-0001. They issued voluntary action indicated (VAI) letters at Sites 111 and 777. A letter for Site 333 has not yet been issued.

At Site 111, the investigator noted that subjects exceeding the maximum age were enrolled, as were subjects who were taking less than the protocol-required minimum dose of 4 mg/day.

At Site 333, although we were initially informed that the person performing oral mucosa inspections was not a medically trained individual, the final DSI recommendation does not find an issue with this aspect of the study. However, DSI found that "drug reconciliation at site 333 was inadequate for most forms of the test article. Of the six forms of the test article, (including four strengths of the film strips and two strengths of the tablet) for site #333 only one (Suboxone 2mg/0.5mg SL tablets) could be reconciled; there were overages or shortages of the remaining five forms of the test article.

At Site 777, the investigator noted that Visits 8 and 9 were two weeks apart, rather than the protocol-specified one week. Additionally, one patient not on Suboxone prior to enrollment appears to have been enrolled. Furthermore, at this site no distinction was made between used and unused drug supplies that were returned by patients.

The inspector concluded that "data generated … may be used in support of the respective indication"

DSI also audited the clinical and analytical portions of Study 20-273-SA, "A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of a 8mg/2mg Film Formulation of Buprenorphine/Naloxone versus Suboxone under Fasting Conditions." No Form 483 was issued at the clinical site, but at the analytic site, the investigators noted some issues, and recommended that "Accuracy of the reported naloxone concentrations for subjects 407 (Period 2) and 443 (all periods) has not been assured due to unresolved chromat6graphic interference in at least half the reportable naloxone values in each period. The naloxone data for these periods should be omitted and bioequivalence should be re-evaluated." This reevaluation is

being performed by Dr. Agarwal. However, because bioequivalence was not previously established for naloxone in this study, the effect of this reanalysis would be unlikely to change the conclusions about the application.

DSI may be asked to contact the site personnel regarding the specific method of administration that was used in the clinical study.

11.2 Implications of Dosing Data

One of the most surprising aspects of the data was the unusual dosing regimens reported by the study subjects in Study RB-07-0001. The labeling for Suboxone and Subutex clearly calls for a single daily dose of medication. All the clinical trials submitted in support of the applications for Suboxone and Subutex involved single daily doses of either buprenorphine sublingual solution or Suboxone or Subutex tablets. I am unaware of any studies demonstrating efficacy of buprenorphine given in multiple divided doses as a treatment for opioids dependence. (The labeling for Buprenex, used for pain in doses of ~0.3 mg/dose, calls for dosing approximately every six hours.) To the contrary, there is a substantial literature advocating dosing take place less often than daily, for example, Monday/Wednesday/Friday. The pharmacology of buprenorphine—both its plasma half-life and its demonstrated duration of blockade of opioid effects—render multiple divided doses pharmacologically illogical. From a behavioral psychology perspective, single daily dosing is considered important in extinguishing the behavior of self-administering drugs of abuse multiple times per day. There is, in short, absolutely no logical reason and no scientific evidence to support multiple divided doses of buprenorphine in this population. Yet, Reckitt Benckiser reported that:

> RBP has recent information from a consumer practices and attitudes survey conducted between August and September 2008 in 321 current Suboxone users covering 41 states. The average length of therapy with Suboxone was 12 months, ranging from 1-72 months. The data indicated that patients may sometimes take ¼ or ½ of a 2/0.5 mg or 8/2 mg Suboxone tablet, and that for patients who take two, three, or four doses throughout the day, the doses are not necessarily the same. Most commonly, respondents took Suboxone twice daily (46%), followed by once daily (29%), three times daily (15%), and four or more times daily (10%). Thus, the data from this survey are consistent with the Division's observation above that only one-third of the patients in study 0001 were taking a single daily dose of Suboxone. The most common first dose reported in the survey included either ½, 1, or 2 of an 8/2 mg tablet. Additionally, 58% of these respondents split tablets to achieve their target daily dose; respondents who split tablets were, on average, taking less Suboxone and less of the 2/0.5 mg tablets compared to those who did not split.

This identifies a significant gap between the evidence supporting the efficacy of this product and the doses being used by patients. The survey reported above does not indicate whether patients are taking their medications as prescribed (and are being instructed to use multiple daily doses) or whether patients are not adhering to the schedule prescribed to them. However, the fact that the vast majority of patients in Study RB-07-0001 were being treated, prior to study entry as well as during the study, with these unusual dosing regimens points to the likelihood that prescribing practices are significantly out of line with the recommendations of the label as well as the recommendations in treatment guidelines provided by SAMHSA, instructions given in training programs, and dosing in controlled clinical trials.

Not only are these doses illogical and possibly counter-productive from a behavioral standpoint, they also create greater opportunities for diversion, because a patient taking the labeled dose of 16 mg/day as a single daily dose would be prescribed 8 mg buprenorphine/2 mg naloxone tablets and would receive a monthly supply of 60 tablets. The same patient taking his medication as four divided doses would require eight (2 mg/0.5 mg) tablets per day and would receive a monthly supply of 240 tablets.

Reports from Reckitt Benckiser's active surveillance program include "street ethnography" interviews that indicate that patients who share or sell their prescriptions are the main source of diverted methadone. Patients may crush and snort their medication, which allows them to use less (and have more to divert) because of improved bioavailability. One report, in the quarterly surveillance report from 1/1/08-3/31/08 (submitted to NDA 20-733 on 6/7/08) noted "Some key informants reported that users who abuse and/or divert Suboxone tend to have physicians that do not monitor their use well. For instance, there was a report of one woman who had been using heroin on top of Suboxone for two years before her physician noticed that she was using apple juice for her urine tests. Apparently, this woman chewed ¼ tablet of Suboxone to hold off withdrawal symptoms while she was working and she would shoot heroin every evening. She then sold the remaining Suboxone to friends who wanted to get high, thereby funding her heroin habit." Other sources, such as internet groups, suggest this is not an uncommon scenario.

12 Labeling

12.1 Proprietary Name Review

Reckitt Benckiser submitted 'buprenorphine/naloxone soluble film' as the proposed established name and 'Suboxone (b) (4) as the proposed proprietary name. The OSE Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Suboxone (b) (4) conditionally acceptable, contingent upon the Office of New Drug Quality Assessment's (ONDQA) determination that (b) (4) is an accurate description of the finished dosage form for this product. Subsequent to that review, ONDQA determined that the final dosage for the proposed product is a "sublingual film" and that the appropriate established name for this product is 'buprenorphine/naloxone sublingual film' based on the definitions found in the Center for Drug Evaluation and Research (CDER) Data Standards Manual and USP.

(b) (4)

DMEPA recommended that the proposed product and the currently marketed Suboxone product could be managed under the name 'Suboxone' and the two products could be differentiated by the dosage form (sublingual tablet vs. sublingual film) of the products.

DMEPA considered the concerns raised by the clinical discipline that Suboxone sublingual film has been found to be more bioavailable than Suboxone sublingual tablets, and that inadvertent substitution may occur if the film and tablet products are managed under the same proprietary name. DMEPA noted, however, that if the differences were so minor that there would not be a dose conversion table in labeling, this did not seem to be a concern significant enough to preclude using the same proprietary name. They commented that many other products currently marketed that use the same root name for different dosage forms and share the same route of administration. In prescribing and ordering, the two products can be identified by specifying the dosage form in relation to the name (i.e. "Suboxone sublingual tablets" vs. "Suboxone sublingual film"), dose ("place 1 tab under the tongue daily" vs. "place 1 film under the tongue daily"), or when specifying a quantity to be dispensed (i.e. "Dispense #30 sublingual tablets" vs. Dispense #30 sublingual films"). They acknowledged that the risk for inadvertent substitution may occur if practitioners are not aware that the film and tablet products are not interchangeable, but did not believe this rendered the Suboxone name unacceptable, recommending that the risk of inadvertent substitution be mitigated through labeling and carton/container labels, possibly to include statements on the pouch labels, carton and insert labeling to alert healthcare practitioners and patients of the differences between the two products.

Reckitt Benckiser's preference is to use a distinct name for the new product. In an email communication, they outlined a number of concerns about having the single proprietary name of "Suboxone" to be used for both the sublingual tablet and the sublingual strip formulations:

1. *Dispensing errors* at the pharmacy such that "patients will not be receiving the medication their physician intended for them."
2. *Additional work* at the pharmacy and physician's office because need for clarifications, which will "generate complaints from pharmacies, physician offices and patients."
3. *Inadvertent switching* between the sublingual strip formulation and generic tablet alternatives that are not determined to be therapeutically equivalent.
4. *Errors in adverse event (AE) reporting* associated with a specific dosage form, with consequences for timely reporting of accurate safety information to the public.

DAARP agrees that inadvertent switching may occur. However, although the products are not bioequivalent, they are similar enough that switching is unlikely to result in severe consequences, and we will include statements in labels and labeling about the lack of bioequivalence, per DMEPA's recommendations. DAARP also would appreciate the ability to distinguish between dosage forms in adverse event reporting; however, DMEPA has indicated that this is not considered a reason for the use of a separate proprietary name.

DMEPA notes that Reckitt Benckiser has the option of proposing an alternate trade name. This would require a new 90 day review, separate from the NDA review clock.

12.2 Physician labeling

At Agency request, Reckitt Benckiser used as base copy for the physician labeling the Suboxone/Subutex label, revised per Agency recommendations. (In some cases, Agency recommended language was modified; these instances were not all identified.) This label, however, is in PLR format and therefore comparisons to the Suboxone/Subutex label are rendered complex.

The major changes recommended to the proposed label include:

1. (b) (4)
2. Addition of sections on "Clinical Supervision" and on the management of "Unstable Patients" to the *Dosage And Administration* section to more clearly convey the appropriate management of patients with this medication, including the need for careful monitoring, frequent visits, and caution concerning quantities of take-home medication. Some of this text appeared elsewhere in labeling but was moved to increase prominence.
3. Revision of a section inserted by Reckitt Benckiser entitled " (b) (4) Because this was the critical safety issue, this section was retitled "Use in Opioid-Naïve Patients" and revised to provide the relevant information (b) (4)
4. Revision of the *Adverse Reactions* section (b) (4)
5. Reorganization of *Controlled Substance, Abuse, and Dependence* sections along the lines of other opioid drugs.
6. Restoration of a statement (which was in the text provided to Reckitt Benckiser by the Agency) noting that buprenorphine/naloxone combinations may be injected by some individuals.
7. Revision of *Nonclinical Toxicology* section to include results of studies reviewed in this application.
8. Addition of a statement about inhibition of CYP enzymes by buprenorphine.
9. Deletion of the description of (b) (4) (This is under discussion because other members of the review team noted that it may be confusing.)

12.3 Carton and immediate container labels

DMEPA has recommended that Reckitt Benckiser remove a [redacted] from the carton and container labels to prevent confusion with Suboxone tablets, and that the net quantity statement on the cartons be revised to more clearly communicate that each pouch contains one film.

In addition, DMEPA expressed concern about the wording of the directions for use, which uses the term [redacted] DMEPA recommends replacing this with "under the tongue." [redacted] However, if Reckitt Benckiser intends for the product to be placed [redacted] of the tongue, the language should be revised to make this more clear.

12.4 Patient labeling/Medication guide

Reckitt Benckiser submitted [redacted] a Medication Guide. They were asked to resubmit a single piece, in Medication Guide format, which has been recently received. It has not yet been reviewed by OSE nor have comments been received from DDMAC. However, it clearly requires some reorganization and revision.

Notably, as discussed above, the Medication Guide contains a section explaining the administration of the filmstrips, [redacted]

Reckitt Benckiser has been asked to clarify how the drug was administered in the trials, and why the administration method pictured in the Medication Guide is being recommended if it differs from the method or methods in the studies.

12.5 Physician and Pharmacist Brochures

As with the NDAs for Subutex and Suboxone, the labeling for this product also includes brochures aimed at physicians and pharmacists. Both brochures provide important background information on the Drug Addiction Treatment Act of 2000 and the procedures required to obtain authorization to prescribe the product. Detailed labeling review has not been completed at the time of this writing because these brochures have only recently been submitted for review.

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend a Complete Response letter be sent delineating the following issues, unless these can be resolved prior to the action date.

13.1.1 Unresolved Issues

1. Need to develop an agree upon a Risk Evaluation and Mitigation Strategy
See below for a description of recommended elements of the REMS.

2. Determination of the clinical significance use of different methods of administration.
As described above, it has recently come to our attention that there may be potentially clinically significant discrepancies among the sponsor's recommended method of administration (in proposed labeling), the method of administration in the clinical pharmacology program, and the method of administration in the clinical safety study. The patient labeling submitted in late June (b) (4) None of the directions in the clinical studies appear to have communicated this clearly. Most concerning, the clinical safety study used directions which imply that the product should be placed on the floor of the mouth.

We have requested that the Division of Dermatology and Dental Products (DDDP) provide an assessment of the potential impact of various administration methods, and an opinion on whether the data from the studies provides support for the use of the product as proposed in labeling. Dr. Frederick Hyman of DDDP has indicated that a number of questions may need to be answered by Reckitt Benckiser before such an assessment can be made. In addition, DSI may be asked to contact the site investigators to inquire directly about the methods of administration.

The Clinical Pharmacology team has also been asked to comment on the potential impact of different administration methods on the pharmacokinetics, to determine whether the PK studies were conducted in a manner that provides information about the PK when the product is used as proposed in labeling.

3. Resolution of any deficiencies that may be identified on facilities inspections which have not yet been completed.
The inspection of the drug substance manufacturing, release testing, and stability testing site in Hull, England is scheduled for 7/22/09.

13.2 Risk Benefit Assessment

The combination of buprenorphine and naloxone in 4:1 ratio, dosed sublingually, has been shown to be safe and effective for the treatment of opioid dependence in the context of NDA 20-732 for Suboxone tablets. This new formulation is a line extension which does not appear to be associated with any unique toxicities not previously identified. Although it is somewhat more bioavailable than the approved tablet formulation, the exposures are expected to be within the range established as safe in the referenced applications for Subutex and Suboxone tablets. The most concerning risks are respiratory depression (chiefly in the setting of intravenous misuse/combination with benzodiazepines), abuse/diversion, accidental pediatric exposure, and potential hepatotoxicity. This is balanced against effectiveness in keeping patients in treatment and keeping them from using illicit drugs, which also carry many of the same risks.

The new formulation offers relatively minor advantages. The more rapid dissolution may be perceived as a convenience to patients. The unit-dose packaging is likely to be an effective deterrent to accidental pediatric exposure, although the more rapid dissolution might increase the likelihood of adverse consequences when accidental exposure does occur.

One other purported benefit is (b) (4)

13.3 Recommendation for Postmarketing Risk Management Activities

Suboxone (buprenorphine/naloxone sublingual tablets) and Subutex (buprenorphine sublingual tablets) were approved in 2002 subject to a risk management program that encompassed:

1. Targeted product distribution and sales monitoring
2. Active surveillance for diversion and abuse (including an advisory group to recommend interventions if problems were identified). This program was extensive, and included surveys of patients, treatment programs, and physicians, as well as a network of "street ethnographers" who collected information about illicit use of buprenorphine directly from individuals involved in the street drug trade.
3. Educational programs for patients, physicians, and pharmacists (n.b., this referred to specific labeling brochures for each of these audiences, approved as part of the labeling).

(b) (4)

(b) (4)

The Risk Management Program was developed prior to the passage of the Food and Drug Administration Amendments Act (FDAAA) and therefore is not enforceable. At the time of approval of this application, a Risk Evaluation and Mitigation Strategy (REMS) under FDAAA should be required.

The specific safety concerns to be addressed include:

1. Accidental pediatric exposures:

   Accidental pediatric exposures to Suboxone and Subutex are reported at a prescription-volume-adjusted rate that exceeds that of other narcotic analgesics. A **MedGuide** strongly communicating the need to keep buprenorphine products out of reach of children is recommended as an appropriate strategy to manage this risk.

2. Increasing reports of abuse, misuse and diversion attributed to patients who receive prescriptions with little supervision or ancillary support towards recovery from drug addiction:

   The post-marketing surveillance program, particularly the "street ethnography" interviews conducted as part of the risk management program note that it is easy to obtain buprenorphine on the street and that the source is usually patients who find it very easy to get excessive supplies of buprenorphine from physicians. Although both labeling and treatment guidelines recommend supervised administration and frequent face-to-face visits, progressing to less intense supervision as treatment progresses, there are reports that physicians provide prescriptions for large supplies of medication on the first visit and do not monitor progress, compliance, or ongoing illicit drug use. Buprenorphine products have not been shown to be safe or effective when used in this manner. Therefore, an **"element to assure safe use"** requiring the sponsor to ensure that patients are monitored appropriately (i.e. in keeping with labeling and SAMHSA guidelines) is recommended as a strategy to ensure safe and effective use and to prevent abuse and misuse. Because physician certification is provided for under the Drug Abuse Treatment Act (DATA) and the responsibility for this certification has been delegated to the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Drug Enforcement Administration (DEA), it does not seem appropriate to create a separate education and certification program to be administered by Reckitt Benckiser. However, despite this provision, it appears apparent that there is widespread disregard of the recommendations for use of the product, in terms of frequency of face-to-face visits, counseling provided, monitoring of results, and also in dosing, with many (if not most) patients receiving multiple daily doses, which are pharmacologically illogical and unsupported by efficacy data, and promote diversion by, in many cases, giving patients more tablets per prescription than would be required with a single daily dose. The objectives of this element of the REMS should be to ensure that the products are used under conditions that ensure safe and effective use,

specifically ensuring that patients are monitored carefully and frequently and provided with necessary counseling, and that medication is provided to patients in appropriate doses and quantities to prevent diversion.

Because the active surveillance program already in place for Subutex and Suboxone has been useful and effective in detecting problems, this should be included as an aspect of the evaluation of the REMS.

13.4 Recommendation for other Postmarketing Study Commitments

It is clear to me that the main safety study submitted in this application was inadequate to characterize the oral mucosal safety of this product. It seems to have been conducted in a cavalier fashion and it is not clear that the product was even placed in the mouth according to the directions now recommended in labeling. Furthermore, without any comparator, it would have been difficult to place findings, had there been any, into context. However, if the consultants in the Division of Dermatology and Dental Products and the Clinical Pharmacology review team determine that the differing methods of administration would not affect either pharmacokinetics or local tolerability, I think that better characterization of the local effects in a more carefully-conducted study could occur as a post-marketing study. The health implications of local mucosal irritation are minor, and while characterization is needed, this risk would be outweighed by the benefit of treatment of opioid dependence. The study should compare the oral mucosal tolerability of the film strip product to that of the sublingual tablet. It should enroll patients who are using the product according to the labeled directions (both dosing and method of product placement in the mouth) and should incorporate oral exams by dental professionals.

Furthermore, the hepatic safety study currently being conducted as a post-marketing commitment under the NDAs for Suboxone and Subutex should be reiterated at this time as a post-marketing requirement.

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

/s/

Celia Winchell
7/15/2009 12:22:25 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Application Number	22-410
Priority or Standard	Standard
Submit Date(s)	October 20, 2008
Received Date(s)	October 21, 2008
PDUFA Goal Date	August 21, 2009
Division / Office	Division of Anesthesia, Analgesia, and Rheumatology Products, ODE II
Reviewer Name(s)	Celia Winchell, M.D.
Review Completion Date	July 2, 2009
Established Name	Buprenorphine and Naloxone sublingual film
(Proposed) Trade Name	Suboxone (b) (4)
Therapeutic Class	Opioid partial agonist
Applicant	Reckitt Benckiser
Formulation(s)	sublingual film
Dosing Regimen	Titrated to effect, usually 16 mg/day
Indication(s)	Maintenance treatment of opioid dependence
Intended Population	Adults

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

See my Cross-Disciplinary Team Leader review, which was post-dates this review and contains my most up-to-date recommendations and assessments of the overall application. This review provides additional detail on the clinical aspects of the application.

2 Introduction and Regulatory Background

Buprenorphine HCl is partial agonist at the μ receptor which has been marketed in the US since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain. In 2002, two sublingual tablet formulations were approved for the treatment of opioid dependence: Subutex (buprenorpine only, NDA 20-732) and Suboxone (buprenorphine with naloxone intended to deter abuse, NDA 20-733). The present NDA proposes a new dosage form of the buprenorphine/naloxone combination product, in a soluble film strip intended for sublingual use.

2.1 Product Information

- Drug established name: buprenorphine and naloxone sublingual film
- Chemical name: buprenorphine hydrochloride and naloxone hydrochloride.
- Proposed trade name: Suboxone (b) (4)
- Drug class: Opioid partial agonist
- Proposed indication: Maintenance treatment of opioid dependence
- Dose: Usual dose 16 mg buprenorphine/day; Titrated to effect in range of 4-24 mg buprenorphine/day
- Age groups: Adults
    - Exempt from PREA due to orphan designation

2.2 Currently Available Treatments for Proposed Indication

Pharmacological treatment of opioid dependence includes both antagonist and agonist therapy.

Antagonist therapy is available using the approved opioid antagonist, naltrexone, marketed as ReVia. The indication for ReVia is "blockade of exogenously administered opioids," noting that data showing an effect on recidivism in opioid dependence is lacking.

Agonist therapies include methadone (Methadose, Diskets, Dolophine, and generics) and buprenorphine (Subutex sublingual tablets) and buprenorphine/naloxone combination (Suboxone sublingual tablets).

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine is available as an0.3 mg/ml injectable solution for pain (Buprenex, NDA 18-401, Reckitt Benckiser, and generics) and as sublingual tablets for opioids addiction (Suboxone, NDA 20-733 and Subutex, 20-732, Reckitt Benckiser; a tentative approval for generic buprenorphine tablets has been issued.)

2.4 Important Safety Issues With Consideration to Related Drugs

Major safety concerns about Suboxone and Subutex tablets include the following:

- Hepatic safety

  At the time of NDA approval in 2002, there was a concern about the potential for buprenorphine to cause hepatic injury, particularly in patients with pre-existing hepatic vulnerability such as viral hepatitis. However, the review of the data at the time of approval was inconclusive regarding the role of buprenorphine in events occurring primarily in a population exposed to many other risks of hepatic injury. Therefore, Reckitt Benckiser was asked to commit to performing a post-marketing study comparing the risks of hepatic events in patients treated with buprenorphine for opiate dependence to patients treated with methadone. This study is ongoing, although it must be noted that it is being conducted by the National Institue on Drug Abuse and not by Reckitt Benckiser.

- Abuse, misuse, and diversion

  Like any opiate, buprenorphine is subject to abuse, misuse and diversion. Although buprenorphine was believed for a time to lack abuse potential, the experience with this drug around the world has clearly demonstrated that it is euphorigenic and is sought out for recreational use. In recognition of this, at the time of approval of NDAs 20-732 and 20-733, the FDA contributed to a recommendation for upscheduling to Schedule III (Buprenex was previously controlled in Schedule IV). However, because Drug AddictionTreatment Act (DATA) of 2000, Suboxone and Subutex are not subject to the limitations placed on methadone treatment, and can be prescribed in doctors' offices for the treatment of opioid dependence, and there are no regulations pertaining to frequency of visits or take-home quantities. Reckitt Benckiser implemented a Risk Management Plan at the time of approval of these products, which included:

1. Targeted product distribution and sales monitoring
2. Active surveillance for diversion and abuse (including an advisory group to recommend interventions if problems were identified)
3. Educational programs for patients, physicians, and pharmacists (n.b., this referred to specific labeling brochures for each of these audiences).

(b) (4)

(b) (4)

Since approval, there have been reports of abuse, misuse and diversion attributed to patients who receive prescriptions with little supervision or ancillary support towards recovery from drug addiction. The post-marketing surveillance program, particularly the "street ethnography" interviews conducted as part of the risk management program note that it is easy to obtain buprenorphine on the street and that the source is usually patients who find it very easy to get excessive supplies of buprenorphine from physicians.

- Accidental Pediatric Exposure

Reckitt Benckiser's monitoring of Poison Control Center reports, as well as analysis from the RADARS surveillance program which monitors a number of other opioids products, reveals that the number of reports involving buprenorphine products is higher than most other opioids analgesics when corrected for volume of distribution. This may reflect the impact of opioid addiction on parental functioning, with patients being treated for addiction less able, as a group, to pay sufficient attention to protecting children in the home from accidental exposure to medication. However, perhaps because of buprenorphine's partial agonist pharmacology and poor oral bioavailability, there have been no fatal cases.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Interaction	Key Points of Discussion
Pre-IND meeting July 25, 2007 (Notably, this was designated by Reckitt Benckiser as "pre-NDA" and they had not planned to conduct their studies under an IND until informed this would be necessary.)	1. A 505(b)(1) submission would be appropriate as all data to be referenced was Reckitt Benckiser's. 2. Standard review would be likely. 3. Reckitt Benckiser's specific CMC questions (many of them of a pre-NDA nature). 4. Need for qualification of a synthesis impurity of naloxone. 5. PK program would need to establish dose-proportionality, demonstrate that intermediate doses could be delivered by combining the available strengths, demonstrate bioequivalence to the approved tablets with complete characterization across the proposed dose strengths. 6. In the case of non-bioequivalence, additional clinical studies could be needed to support the safety or efficacy of the new products. 7. Safety data would be needed because the sublingual film strip is a novel dosage form/route. 8. Information would be needed to inform the appropriate use of multiple film strips necessary to deliver intermediate doses. (For example, explore the practicality of placing several film strips under the tongue simultaneously, and/or explore the necessary time between dosing if strips must be placed sequentially.) (b) (4) 10. In response to the sponsor's proposal that (b) (4) Reckitt Benckiser was informated that if the studies demonstrate that the Cmax and AUC from the film strip products are lower than from the sublingual tablet products, this would raise concerns about the efficacy of the new product and efficacy studies might be needed. Conversely, markedly higher plasma levels from the film strip product would raise safety questions. However, it is our expectation that safety issues with higher exposure of buprenorphine could be addressed with reference to data from studies on the sublingual ethanol solution, included in the Subutex and Suboxone NDAs**.** **(continued)**

	11. Local tolerability would need to be addressed, including a safety database with a minimum of 100 patients using the film strip products over several months of treatment, involving assessments of the oral mucosa by qualified assessors. Naltrexone-blocked volunteers would not contribute to the 100 needed. 12. Substantially greater absorption of naloxone from the film strip products compared to the Suboxone tablets might pose a greater risk of precipitating withdrawal, with implications for treatment retention and, ultimately, for efficacy. In this circumstance, data on treatment efficacy may be necessary, related primarily to precipitation of withdrawal early in treatment, and the impact this would have on getting patients successfully stabilized on buprenorphine. 13. Because this product involves the same active moiety and the same indication as the products for which Reckitt Benckiser received Orphan Status designation, this product would also be considered to have Orphan Status and the pediatric study requirements of the Pediatric Research Equity Act would not apply.
IND 75,810 and 75, 811 submitted August 29, 2007	IND opened with PK studies in naltrexone-blocked volunteers.
Pre-NDA meeting June 24, 2008	(b) (4) 2. Reckitt Benckiser was advised to submit either a new proprietary name or the name Suboxone with a modifier (b) (4) along with the data from a failure mode and effects analysis showing which approach would be less error-prone, to support their proposal. 3. Because plasma naloxone levels with the film strip combination product have been shown to be higher than those with Suboxone additional efficacy data from a study in outpatients, showing that the differences between formulations did not translate to differences in the proportion of patients able to become successfully stabilized (e.g. induction through the first several weeks of treatment) on buprenorphine.would be needed to support the application. Study US-07-0002, being conducted in an inpatient setting, is unsuitable for determining whether patients are more or less likely to drop out of treatment prior to completing induction/stabilization when treated with the new formulation than with the old formulation. **(continued)**

	4. Preliminary data from Study RB US-07-0002 showed hat symptoms consistent with precipitated withdrawal occurred in two of eight study subjects. This further raised concerns. 5. These concerns were to be addressed by Reckitt Benckiser's proposal to submit the product only for maintenance use, in patients already stabilized on tablet formulations of buprenorphine. The possibility that the data would not support this was identified as a review issue. 6. In preparing the ISS, COSTART and MedDRA terminology were not to be used interchangeably. MedDRA terms were to be mapped to COSTART terms, in order to compare the safety findings from the new formulation to the established safety profile for Subutex/Suboxone, and any inconsistencies discovered were to be discussed. 7. It was strongly recommend that maximum real-time stability data be provided in the NDA. Expiration dating would be estimated as per ICH Q1E, based on real-time pivotal and supporting data and statistical analysis, as applicable. 8. Available data demonstrated that the film strip administered by sublingual or buccal route and the approved sublingual tablet formulation are not bioequivalent. Additional studies would not be necessary to address bioequivalence of film strip to the approved sublingual tablets. 9. (b) (4) 10. If only 2-mg and 8-mg doses would be available, additional bioequivalence data would be needed (e.g., assess whether 2-mg + 2-mg + 8-mg is equivalent to 12-mg of Suboxone). 11. The lack of specific dental training of evaluators assessing oral mucosa was a concern but would be unlikely to preclude approval; a post-marketing study could be needed. 12. A section of the NDA should specifically address hepatic safety. 13. A Risk Mitigation and Evaluation Strategy (REMS) would be needed with the NDA submission.

2.6 Other Relevant Background Information

The Orphan Exclusivity granted to Suboxone and Subutex at the time of approval will expire in October, 2008. Reckitt Benckiser, among others, has expressed grave concern that the availability of generic buprenorphine sublingual tablets will lead to greater diversion and abuse. The introduction of this product appears to be intended to provide the company with a line extension product, (b) (4)

Reckitt Benckiser makes the following assertions about the benefits of the proposed product, including (applicant's language quoted below, followed by reviewer comment):

- Use of child-resistant packaging in unit dose format for additional protection against unintentional pediatric exposure,
- Protection against counterfeiting,
- Protection against diversion, by providing a dosage form that is very difficult for the patient to remove from the sublingual mucosa once it is administered. This will provide assurance to the caregiver that the dose has actually been taken appropriately in a supervised setting.
- Improved patient convenience,
- Provision of a robust unit dose product for hospital and institutional use,
- Decreased product damage during shipping as compared to Suboxone tablets

These claims will be addressed in the review below as appropriate. Briefly, accidental pediatric exposure is a concern for the buprenorphine sublingual tablets currently marketed. There is potential for child-resistant, unit-of-use packaging to be beneficial in this regard. However, as will be discussed below, the Applicant has reported that it is common for patients to divide their doses into fractions for use. Therefore, partial doses left out of the child-resistant packaging may still represent a risk. Furthermore, the more rapid dissolution of this dosage form compared to the tablets, and the difficulty of spitting it out once it is placed in the mouth, could actually contribute to more severe outcomes when the product is accidentally taken by a small child.

Regarding protection against diversion in supervised settings via removal from the mouth, Suboxone is not generally administered in a supervised setting after initial stabilization of patients, and "cheeking" of medication is not identified as a source of diverted medication; therefore the difficulty of removing the product from the mouth once administered is unlikely to have any discernible effect on diversion of this product.

Regarding patient convenience, the doses proposed for marketing in this application are only the 2 mg buprenorphine/0.5 mg naloxone strip and the 8 mg buprenorphine/2 mg naloxone strip, representing little clinical improvement over the existing products other than more rapid dissolution.[1]

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A number of issues were encountered in the review of this application.

Tables with errors, various text-to-table discrepancies, and other inconsistencies were identified throughout the review and required re-submission of corrected material. As an example, Reckitt Benckiser required several re-explanations before they were able to submit a table delineating the extent of exposure in a dose-by-duration format, or a table identifying how many patients had completed the full number of protocol-specified visits and oral exams. Analyses were submitted that appeared to have been generated without consideration given to the clinical meaningfulness of the presentations. The dataset of adverse events for the clinical pharmacology program did not identify the treatment assignment associated with the adverse event in crossover studies. Tables were submitted that "integrated" laboratory data from Study RB-US-07-0002 with Study RB-US-07-0001, where no laboratory data was collected. Analyses of oral exams excluded "out of window" exams, which included all exams conducted at one of the clinical sites.

One other notable issue identified was the design of the Case Report Form for Study RB-US-0001. The CRF was ambiguously worded, such that the total daily dose and the dosing regimen for Suboxone prior to study start were recorded in different ways by different study personnel, and it was impossible to determine in all cases the exact dosing regimen. Furthermore, the CRF did not capture the dosing regimen *during* the study at all. There were also unusual aspects of the way the CRF captured reason for study discontinuation, offering no option for "adverse event."

As noted below in the discussion of oral mucosal safety, the glaring lack of abnormal findings from the exams during study RB-US-07-0001, in contrast to the findings in study RB-US-07-0002, raises questions about the attention to detail in collection of this data.

[1] Reckitt Benckiser initiated development programs for (b) (4) buprenorphine/naloxone combination strips. (b) (4) four doses, containing 2 mg, 8 mg, 12 mg, and 16 mg of buprenorphine respectively, were tested clinically. The approved products are available only in tablets containing 2 mg or 8 mg of buprenorphine. The dose recommended in labeling for the sublingual tablets is 16 mg/day as a single daily dose and requires dosing with two 8 mg tablets simultaneously. Therefore, the availability of higher doses would have contributed to patient convenience and may have reduced diversion, but these higher doses were not ultimately proposed for marketing.

3.2 Compliance with Good Clinical Practices

The Division of Scientific Investigation (DSI) was asked to inspect all three sites of Study RB-07-0001. They issued voluntary action indicated (VAI) letters to Sites 111 and 777. A letter to Site 333 has not yet been issued.

At Site 111, the investigator noted that subjects exceeding the maximum age were enrolled, as were subjects who were taking less than the protocol-required minimum dose of 4 mg/day.

At Site 333, although we were initially informed that the person performing oral mucosa inspections was not a medically trained individual, the final DSI recommendation does not find an issue with this aspect of the study. However, DSI found that "drug reconciliation at site 333 was inadequate for most forms of the test article. Of the six forms of the test article, (including four strengths of the film strips and two strengths of the tablet) for site #333, only one (Suboxone 2mg/0.5mg SL tablets) could be reconciled; there were overages or shortages of the remaining five forms of the test article.

At Site 777, the investigator noted that Visits 8 and 9 were two weeks apart, rather than the protocol-specified one week. Additionally, one patient not on Suboxone prior to enrollment appears to have been enrolled. Furthermore, at this site no distinction was made between used and unused drug supplies that were returned by patients.

The inspector concluded that "data generated … may be used in support of the respective indication"

3.3 Financial Disclosures

Appropriate financial disclosures were submitted for the investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The product is a pale orange 0.875" x 0.5"soluble film strip film which reportedly "hydrates readily to a gel form (within about 30 seconds) upon application to the oral mucosa [with] subsequent erosion over approximately three minutes." (The current Suboxone sublingual tablets take up to 10 minutes to completely disintegrate sublingually in some patients.) It contains lime flavoring, similar to the flavor that was utilized in Suboxone sublingual tablets, to disguise the bitter taste of the active ingredients.

The two dosage strengths of buprenorphine and naloxone soluble films are produced from separate film formulations. A low strength film formulation, Suboxone (b) (4) (2 mg buprenophine/ 0.5 mg naloxone) soluble film, is used to produce the buprenorphine and naloxone soluble film 2 mg/ 0.5 mg dose strength and a high strength film formulation,

Suboxone (b) (4) (8 mg buprenophine/ 2 mg naloxone) soluble film, is used to produce the buprenorphine and naloxone soluble film 8 mg/ 2 mg dosage strength product.
The soluble films are 0.875" x 0.5" for both dose strengths. The weights of the 2 mg/0.5 mg and 8 mg/2 mg soluble films are 39 mg and 50 mg respectively. For the 12 mg and 16 mg doses used in the clinical trials (but not proposed for marketing) the buprenorphine /naloxone 8/2mg film strip buffered to pH 3 was utilized to produce the two higher strength film strips by cutting the bulk film to longer length film pieces.

This is significant because the clinical trials were conducted with one dose of the low-strength film (2 mg/0.5 mg) but three different doses of the high-strength films (8 mg/2 mg; 12 mg/3 mg; and 16 mg/4 mg). However, only one of these three is proposed for marketing (8 mg/2 mg). (b) (4)

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No significant safety/efficacy issues.

4.4 Clinical Pharmacology

Much of the text below is from the Clinical Pharmacology Review and presentations prepared by Dr. Sheetal Agarwal.

4.4.1 Mechanism of Action

Buprenorphine, the primary active compound in Suboxone (b) (4) (as well as in Suboxone sublingual tablets), is a partial opioid agonist with a high affinity for the mu-opioid receptor and lower intrinsic activity than full opioid agonists. Naloxone (an antagonist at the mu-opioid receptor) is included in the formulation to discourage diversion and abuse of Suboxone Tablets and (b) (4) The primary purpose of inclusion of naloxone in these products is to prevent the intravenous misuse of buprenorphine (concept originally used in currently marketed pentazocine product, Talwin NX). This could be done because naloxone exhibits poor oral and sublingual bioavailability. Therefore, if Suboxone (b) (4) is misused or abused by injection, the naloxone component is expected to antagonize the opioid agonist effects of buprenorphine and potentially precipitate withdrawal in an individual dependent on full opioid agonists and therefore discourage the individual to abuse the product.

4.4.2 Pharmacodynamics

(This text is from the labeling for Subutex and Suboxone.)

Subjective Effects:

Comparisons of buprenorphine with full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In non-dependent subjects, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo, and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced, non-dependent subjects. Both drugs produced typical opioid agonist effects. For all the measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administrations. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in intravenous (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to non-dependent subjects to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared with placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin-dependent subjects, intravenous administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

4.4.3 Pharmacokinetics

Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both C_{max} and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the pharmacokinetic parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours.

Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone16 mg	Subutex 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

This application rests primarily on pharmacokinetic linkage of the proposed product to the approved product. The Clinical Pharmacology package submitted for this NDA consisted of 19 Phase 1 pharmacokinetic (PK) studies conducted in healthy adult volunteers (including pilot, pivotal bioequivalence (BE) and dose and dosage form proportionality studies, studies with other strengths of Suboxone (b) (4) that are not sought for approval, (b) (4) . Out of the 19 PK studies submitted, 7 were deemed relevant for this NDA and were reviewed. Out of the 7 studies reviewed, 4 were thoroughly reviewed because they form the basis of approval for the subject matter of this NDA and the other 3 are considered additional supportive studies. The other 10 PK studies submitted included testing of (b) (4) and the buccal route of administration for (b) (4) the (b) (4) Suboxone (b) (4).

The seven relevant studies include studies comparing one dose of strip to a comparable dose of Suboxone tablet (20-250-SA and 20-273-SA), studies comparing various combinations to yield intermediate doses such as 4 mg (2 x 2 mg) or 12 mg (8 mg plus 2 x 2 mg), somewhat less-relevant studies of the doses not proposed for marketing (12 mg and 16 mg strips) compared to equivalent doses of tablets, and a dose-proportionality study of various doses of Suboxone (b) (4) These are listed below.

- Study 20-250-SA: 2/0.5 mg strips vs. tabs
- Study 20-273-SA: 8/2 mg strips vs. tabs
- Study 20-272-SA: 2 x 2/0.5 mg strips vs. tabs
- Study 10033995: 1 x 8/2 mg + 2 x 2/0.5 mg strips vs. tabs
- Study 20-B90-SA: 12/3 mg strips vs. tabs
- Study 20-A90-AU: 16/4 mg strips vs. tabs
- Study 20-291-SA: Dose proportionality of the 2/0.5, 2 x 2/0.5, 8/2, 12/3 and 16/4 mg strips

In the tables below, Dr. Agarwal summarizes the Cmax and AUC data for each study[2] and provides a 90% confidence estimate of the relative bioavailability. Note that the criteria for bioequivalence (confidence estimate falling between 80-120%) is not met in several studies. Buprenorphine exceeds criteria for BE limits in several studies; naloxone exceeds criteria to a greater degree. Values outside these limits are shown in the tables below using italics.

(b) (4)

Study 20-250-SA: 2/0.5 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**0.78 ± 0.32**	**0.95 ± 0.27**	**121.66**	**112.62 –** ***131.43***
Bup AUC inf (ng*h/mL)	**7.65 ± 2.65**	**8.65 ± 2.85**	**114.22**	**106.65 – 122.32**
Nal Cmax (pg/mL)	**51.3 ± 21.1**	**54.1 ± 23.0**	**104.01**	**95.79 – 112.93**
Nal AUC inf (pg*h/mL)	**124.2 ± 52.5**	**137.3 ± 43.1**	**107.28**	**96.98 – 118.69**

Study 20-272-SA: 4/1 mg (2 x 2/0.5 mg) strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**1.34 ± 0.57**	**1.40 ± 0.68**	**104.61**	**94.58 – 115.69**
Bup AUC inf (ng*h/mL)	**12.46 ± 4.64**	**13.71 ± 5.88**	**104.55**	**96.42 – 113.37**
Nal Cmax (pg/mL)	**70.8 ± 34.7**	**69.8 ± 37.8**	**100.86**	**90.95 – 111.84**
Nal AUC inf (pg*h/mL)	**204.6 ± 114.9**	**204.3 ± 108.4**	**106.48**	**93.26 – 121.58**

Study 20-273-SA: 8/2 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**2.58 ± 1.10**	**3.37 ± 1.80**	***127.8***	**116.11 –** ***140.66***
Bup AUC inf (ng*h/mL)	**25.31 ± 9.50**	**30.45 ± 13.03**	**119.51**	**110.28 –** ***129.51***
Nal Cmax (pg/mL)	**135.0 ± 57.3**	**193.0 ± 91.2**	***141.04***	***126.87 – 156.80***
Nal AUC inf (pg*h/mL)	**374.6 ± 132.8**	**480.8 ± 201.0**	**121.19**	**108.44 –** ***135.44***

Study 10033995: 12/3 mg (1 x 8/2 mg + 2 x 2/0.5 mg) strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**3.44 ± 1.53**	**4.05 ± 2.63**	**115.05**	**106.44 – 124.35**
Bup AUC inf (ng*h/mL)	**37.11 ± 14.14**	**40.50 ± 15.93**	**111.21**	**105.62 – 117.09**
Nal Cmax (pg/mL)	**170.0 ± 77.6**	**207.0 ± 143.0**	**117.24**	**106.80 – *128.71***
Nal AUC inf (pg*h/mL)	**524.0 ± 253.6**	**582.7 ± 324.9**	**110.47**	**102.90 – 118.60**

Study 20-A90-AU: 16/4 mg strips vs. tabs

	SL tab	*SL strip*	*Geometric Estimate*	*90% Confidence Interval*
Bup Cmax (ng/mL)	**4.51 ± 1.51**	**5.47 ± 1.99**	***133.64***	**117.52 – *151.98***
Bup AUC inf (ng*h/mL)	**47.31 ± 13.81**	**58.53 ± 20.59**	***132.50***	**120.63 – *145.54***
Nal Cmax (pg/mL)	**259.0 ± 200.0**	**324.0 ± 231.0**	***143.79***	**116.86 – *176.92***
Nal AUC inf (pg*h/mL)	**677.7 ± 366.4**	**930.4 ± 421.3**	***137.71***	**121.19 – *156.49***

Study 20-291-SA: Dose proportionality of the 2/0.5, 2 x 2/0.5, 8/2, 12/3 and 16/4 mg strips
Buprenorphine

	2/0.5	2*2/0.5	8/2	12/3	16/4
Cmax (ng/mL)	**1.07**	**1.66**	**3.55**	**4.80**	**6.05**
AUClast (hr*ng/mL)	**7.18**	**13.42**	**28.71**	**39.86**	**50.32**
AUCinf (hr*ng/mL)	**8.43**	**14.62**	**30.66**	**41.74**	**53.40**

Naloxone

	2/0.5	2*2/0.5	8/2	12/3	16/4
Cmax (pg/mL)	**48.5**	**72.8**	**193**	**286**	**401**
AUClast (hr*pg/mL)	**100.6**	**164.1**	**442.9**	**647.5**	**937.9**
AUCinf (hr*pg/mL)	**105.1**	**171.0**	**454.8**	**665.1**	**958.4**

In summary, the lower strength film (used to make the 2 mg/0.5 mg Suboxone strip) is bioequivalent to the 2 mg/0.5 mg Suboxone tablet, but the higher strength film, as 8 mg/1 mg Suboxone (b) (4) does not appear to be BE to the 8 mg/1 mg Suboxone tablet. The high-side failure is particularly notable when one 16 mg strip ((b) (4)) is compared to two 16 mg tablets. (b) (4) . At this dose, the mean AUC and Cmax are 30-40% higher than for the tablet. My clinical impression is that dose adjustment might be necessary for patients transitioning from one product to another, although the existing safety database including data from the sublingual solution studies still provides support for use of this more bioavailable product at the currently-labeled doses.

5 Sources of Clinical Data

The application is based on five sources of information:

1. Pharmacokinetic studies in naltrexone-blocked healthy volunteers, comparing the new product to the approved products.
2. Reference to efficacy and safety information included in Reckitt Benckiser's approved applications for Subutex and Suboxone.
3. A single open-label safety study in patients already using Suboxone, intended to evaluate the local tolerability of the new formulation, because no previous experience with sublingual film strips is available to establish the safety of this dosage form.
4. A small inpatient laboratory study comparing the initiation of dosing with Suboxone (b) (4) to initiation of dosing with a buprenorphine-only film strip.
5. Post-marketing data and literature regarding buprenorphine products.

5.1 Tables of Studies/Clinical Trials

Study	Main Features	Enrollment	Comments
RB-US-07-001	12 week, open-label study in patients already stabilized on Suboxone; AEs and oral mucosal exams at clinic visits.	194	
RB-US-07-002	Inpatient, five days of buprenorphine treatment after a period of morphine stabilization. Compared Suboxone (b) (4) to buprenorphine strip; Labs, EKGs, mucosal exams, AEs.	49 enrolled; 38 treated with Suboxone strip or buprenorphine strip.	
Clinical Pharmacology Program (17 studies) (See Clinical Pharmacology review for full table of studies)	Crossover studies; Subjects under naltrexone blockade; Maximum exposure 3 doses	Subutex (N=206) Buprenorphine Soluble Film (N=351) Suboxone (N=266) Suboxone (b) (4) (N=412)	Only SAEs and AEs relevant to oral tolerability reviewed

5.2 Review Strategy

No new efficacy data was provided in this application. Study RB-US-0002, purporting to provide reassuring information on the impact of increased naloxone exposure with Suboxone (b) (4) on the ability to successfully stabilize patients on buprenorphine therapy, was reviewed despite the suboptimal design to determine whether there was evidence of precipitated withdrawal.

Safety data from Studies RB-US-07-0001 (adverse events, oral mucosal exams) and RB-US-07-0002 (adverse events, oral mucosal exams, labs) were reviewed, augmented by data on SAEs and oral mucosal adverse events from the clinical pharmacology program.

A review of literature and postmarketing experience with Suboxone and Subutex was also conducted looking specifically at hepatic safety, use in pregnancy, and accidental pediatric exposure.

This review was performed in collaboration with Dr. Elizabeth Kilgore, whose review addresses the three specific safety issues, incorporating literature/postmarketing findings as well as data from the development program.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study RB-US-07-0001

A detailed description and review of Reckitt Benckiser's safety study, Study RB-US-07-0001 can be found in Appendix 9.2

Briefly, this study was designed to recruit patients "from the pool of patients being treated at the clinical site for opioid dependence who are on maintenance buprenorphine/naloxone sublingual tablets," and to randomize them to use the investigational product either sublingually or buccally for the next 12 weeks, during which AEs would be collected and oral mucosal exams performed at biweekly visits. Safety data from this study were evaluated with a focus on spontaneously-reported adverse events and findings of oral mucosal exams. Primary attention was given to the subset of patients assigned to use the study medication by the sublingual route, as the buccal route has not been proposed in the submitted labeling.

A total of 194 subjects from three study centers were screened and subsequently randomized to treatment with buprenorphine and naloxone soluble film via sublingual administration. (An additional 188 subjects were assigned to treatment by the buccal route. This group does not provide information relevant to the method of use claimed in this application and will generally not be discussed further.) Overall, 99% of the subjects were white, 64% of the subjects were male, and the average age was approximately 36 years (range 19-71 years), with over half of the participants in the 21-35 age group. At baseline, 99% had no oral mucosal abnormality.

Of 194 subjects randomized, 61% were considered "completers," defined as subjects who completed at least 84 days of buprenorphine and naloxone soluble film therapy, with a clinic visit not more than seven days after last soluble film administration. Most common reasons for discontinuation were loss to follow-up and withdrawal of consent. Information pertinent to adverse events leading to discontinuation was recorded in two different places; at Agency request, Reckitt Benckiser provided a tabulation using both sources of information that was used to create the (reviewer-constructed) subject disposition table below, which illustrates that adverse events were not frequently cited as the reason for study drug discontinuation.

	N	%
Randomized	194	
Treated (at least one dose)	194	100%
Completed all study visits	125	64%
Statistical Analysis Plan-defined completers[a]	118	61%
Recorded as "discontinued due to an adverse event" on study termination page (not in CRF)	5	3%
AE listed in CRF listed with action "study medication permanently discontinued"	4	2%
Withdrawn from study (CRF)	63	32%
Subject withdrew consent	12	6%
Investigator decision	10	5%
Sponsor decision	8	4%
Protocol violation	2	1%
Lost to follow-up	17	9%
Other	19	10%
incomplete termination data	1	1%

[a]Excludes major protocol violators

5.3.1.1 Extent of Exposure

The table below illustrates the cumulative exposure to the experimental product. This shows that there are 126 patients exposed for 12 weeks at any dose. Considering only those using the product in the labeled range (generally 12 mg-16 mg), there appear to be fewer than 80 patients contributing three months of safety data. Also, as discussed more thoroughly in the review of the individual study in Appendix 9.2 virtually none of the patients took their medication as recommended in the labeling, as a single daily dose. Furthermore, although 12 mg/3 mg and 16 mg/4 mg strips were available for the clinical trial, they are not proposed for marketing. The currently-marketed product, Suboxone tablets, is available only in 2 mg/0.5 mg and 8 mg/2 mg formulations, so that patients taking the labeled dose of 16 mg/day are to use two tablets simultaneously, as was done in the clinical trial supporting approval of the tablet. In the film strip study, however, any patient using a single daily dose of 16 mg would have been provided with 16 mg strips, so there is likely to be essentially no data on using the film strip product as recommended in labeling, namely, two 8 mg strips sublingually used simultaneously.

Table 14.6.1.11 Cumulative Time on Dose by Dose Level in Study RB-US-07-0001
(Safety Set)

Treatment: Suboxone [redacted] Sublingual (N=194)

	Number of weeks on dose											
Dose Buprenorphine/Naloxone(mg)	1	2	3	4	5	6	7	8	9	10	11	12
At least 2	179	176	176	164	164	158	158	152	152	141	139	126
At least 4	177	174	174	162	162	158	158	152	152	141	139	126
At least 6	168	165	165	153	153	149	149	143	143	131	128	118
At least 8	163	161	160	149	149	145	145	139	138	126	124	114
At least 10	118	117	117	107	104	100	98	93	93	85	83	77
At least 12	115	114	113	104	102	99	98	93	93	85	83	77
At least 16	109	108	107	100	99	96	95	90	90	82	80	74
At least 17	63	63	61	56	56	47	45	39	39	36	35	31
At least 18	62	62	61	56	56	47	45	39	39	36	35	31
At least 20	62	62	61	56	56	47	45	39	39	36	35	31
At least 24	61	61	60	56	56	47	45	39	39	36	35	31
At least 28	14	14	12	10	10	8	8	6	6	4	4	3
At least 32 or more	14	14	12	9	9	7	7	5	5	4	4	3

5.3.2 Study RB-US-07-0002

This was a 34-subject inpatient study intended to demonstrate that neither buprenorphine nor buprenorphine/naloxone soluble film formulation would precipitate an opioid withdrawal syndrome during initiation of treatment. Subjects were initially stabilized on morphine and then underwent challenge sessions with naloxone and placebo to ensure that subjects could detect opioid withdrawal. Subjects who met the criteria to continue in the study were randomized to treatment with buprenorphine soluble films or buprenorphine/naloxone films. Treatment with buprenorphine was initiated with several divided doses of 4 mg each (as is the recommended practice for office induction) totaling 12 mg the first day, with subsequent dosing of 16 mg-24 mg/day as a single daily dose for four additional days. Subjects were evaluated for the severity of withdrawal symptoms using physiological and behavioral measures. Safety measures included adverse events (AEs), oral mucosa exams, vital signs, electrocardiogram (ECG), and clinical laboratory measures (chemistry, hematology, and urinalysis).

Of 79 subjects screened, 49 were eligible and entered the morphine maintenance phase. Ten subjects were not randomized to treatment with buprenorphine or buprenorphine/naloxone films, either because they did not meet criteria for being able to detect withdrawal during the naloxone challenge session or for other reasons, and one subject who was randomized withdrew before receiving buprenorphine. Therefore, baseline data on 49 subjects and on-treatment data on 38 subjects (20 buprenorphine, 18 buprenorphine/naloxone) are available. Of these, 31 subjects (16 buprenorphine, 15 buprenorphine/naloxone) completed five days of treatment with the soluble films. These subjects do not change the extent of exposure tabulation given above because none were on study drug as long as one week.

The data from this study were included in the review of oral mucosal tolerability, and provide the only data on vital signs, ECGs, and clinical laboratory measures in patients not on naltrexone blockade.

5.3.3 Clinical Pharmacology Program

The clinical pharmacology program was conducted in healthy volunteers under naltrexone blockade. Therefore, the overall safety findings from this program do not reflect the safety profile of buprenorphine as it is used in the target population, both because of the concomitant use of naltrexone, and because of the difference in tolerance to opioids. I did not review the overall adverse event profile but focused on local tolerability, and also reviewed the serious adverse events for any possibly relevant cases.

6 Review of Efficacy

No new efficacy studies were included in this application. There was no statistical review of the clinical data.

The efficacy data and recommendations for dosing are based on the approved application for Suboxone, NDA 20-733. A summary of the efficacy studies supporting that application is included in Appendix 9.3. Briefly, the application rested on two studies of buprenorphine sublingual solution that demonstrated the efficacy of an 8 mg/day dose of buprenorphine sublingual solution, which was roughly equivalent to a 12 mg/day dose delivered in a tablet formulation. A single, very brief (four week), placebo-controlled study using the buprenorphine/naloxone combination tablet demonstrated that the dosing regimen (8 mg buprenorphine tablet on day one, 2 x 8 mg buprenorphine tablet on day two, and 2 x 8 mg buprenorphine/naloxone combination tablet thereafter) was effective. These three studies taken together were considered sufficient to support approval of the buprenorphine/naloxone sublingual tablet, Suboxone. No new efficacy studies have been submitted to support the approval of the Suboxone film strip, as Reckitt Benckiser hoped to demonstrate bioequivalence or (once bioequivalence was not demonstrated for all strengths) argue that the differences between the tablet and film strip products were of no clinical significance.

It should be noted that we alerted Reckitt Benckiser to concerns that higher bioavailability of the naloxone component in the film strip formulation compared to the Suboxone tablet could raise concerns about efficacy. This is because naloxone, although poorly bioavailable orally and sublingually and *theoretically* inactive when the product is used as directed, is absorbed to some degree sublingually and could potentially precipitate withdrawal in opioid-dependent patients. However, because buprenorphine binds with high affinity to the opioid receptor, it has been noted that naloxone does not compete effectively with buprenorphine. (Initial attempts to induce naloxone-precipitated withdrawal in buprenorphine-dependent animals and humans were unsuccessful, leading to the misleading conclusion that buprenorphine did not produce dependence. High doses of naloxone are required to reverse the effects of buprenorphine.) Therefore patients dependent on buprenorphine are unlikely to be vulnerable to precipitation of withdrawal by naloxone. The clinical study of Suboxone relied upon for approval of the tablet formulation used Subutex for the initial two days of treatment, so that patients were not transitioned directly from full agonists to the combination product. (b) (4) Notably, the product was studied only in patients already stabilized on buprenorphine and the proposed labeling also stipulates that it is not intended for initial treatment. This is intended to finesse the question of whether the higher naloxone plasma levels seen after sublingual film strip use compared to Suboxone will create an important clinical difference with regard to efficacy.

6.1 Study RB-US-07-0002

Because the comparative bioavailability studies showed that the naloxone exposure after Suboxone (b) (4) administration was higher than after Suboxone tablet administration, the Division was concerned that the amount of naloxone delivered could have an impact on the ability of patients to successfully transition from illicit drug use to maintenance treatment with buprenorphine. Study RB-US-07-0002 was intended to answer this question but the design was unsuitable to address our concerns. The study focused on group mean measures of withdrawal on the Clinical Opiate Withdrawal Scale (COWS). However, the Division expressed the opinion that the most important question was whether any differential naloxone level would translate into decreased likelihood of a patient completing induction and becoming successfully stabilized on a dose of buprenorphine/naloxone. Therefore, the study that was submitted does not directly answer the question.

However, the data submitted from this study do provide some insight into the experience of patients transitioning from a full agonist (morphine) to (b) (4) the buprenorphine/naloxone combination strip. The results were inspected but not reviewed in detail.

RB-US-07-0002 was an inpatient, double blind, single site, randomized trial intended to compare buprenorphine soluble films to buprenorphine/naloxone soluble films for induction (initial treatment) of opioid dependent subjects. Initially, subjects received 30 mg of morphine subcutaneously (SQ) up to 4 times per day for up to 13 days. During morphine maintenance, subjects underwent two laboratory test sessions, during which the subject received a challenge of naloxone (0.4 mg) or placebo intramuscularly (IM) and was evaluated for the severity of withdrawal using the Clinical Opiate Withdrawal Scale (COWS), the Clinical Institute Narcotic Assessment (CINA), visual analog scales (VAS), and pupil diameter measurements establish sensitivity to detect opioid withdrawal effects. Subjects who did not have withdrawal in response to naloxone challenge were ineligible to continue. Eligible subjects were randomized to treatment with 5 days of buprenorphine soluble films or buprenorphine/naloxone soluble films. The first day of dosing, participants received 4 mg buprenorphine (or 4 mg buprenorphine/1 mg naloxone) at 0900, 1100, and 2000 hours. (The use of 4 mg doses repeatedly as needed during the first day of dosing is a commonly-used, although not labeled, induction procedure.) Thereafter, dosing was titrated from 12 mg, once per day at approximately 0900 hours to 16-24 mg/day as a single daily dose.

Prior to and after each day's soluble films administration, subjects were evaluated for the severity of withdrawal symptoms. Reckitt Benckiser's conclusions concerning the mean indicators of withdrawal were that

> "There were no significant differences between the buprenorphine and buprenorphine/naloxone groups in baseline or peak COWS scores; however, there was a statistically significant reduction ($p<0.0001$) between baseline and peak scores. The baseline mean (SD) COWS scores for subjects in the buprenorphine group was 9.1 (5.5) and for that of the buprenorphine/naloxone group of 10.4 (6.4). Scores of 5 to 12 are considered mild; however, some subjects were experiencing moderate levels of withdrawal (COWS scores of 13 to 24). The mean peak COWS scores (SD) in the 23.5 hr

period after the first soluble film administration were 4.2 (2.4) and 5.7 (3.2) for the buprenorphine and buprenorphine/naloxone groups, respectively. COWS scores continued to stay low (below the cutoff for mild withdrawal) on the second day of induction, as well as during the 3 day period following induction (mean peak scores of 1.3 for buprenorphine and 2.6 for buprenorphine/naloxone."

Notably, these calculations excluded subjects who dropped out during the first day of treatment, which is when precipitated withdrawal is most likely.

Two subjects in each treatment arm discontinued during the first day of soluble film dosing. Only two of these were coded as discontinuing due to adverse events, but all four discontinued in similar circumstances, namely, withdrawal symptoms experienced during the first day of induction. Because buprenorphine is to be initiated when patients are already in some degree of withdrawal, the experience of withdrawal is to be expected. Data included in the final study report indicate that, for two of the patients, withdrawal scores were slightly higher one hour after study drug administration than prior to administration, and for one, the score was unchanged. Three of the four withdrew after the second dose of soluble film, which makes precipitated withdrawal somewhat less likely an explanation than had the events occurred after the first dose. It must also be noted that the descriptions of the events ("low tolerance for withdrawal symptoms" or "subject reported being uncomfortable with withdrawal symptoms") and the coding of discontinuation as being due to subject decision (vs. either AE or lack of efficacy) may reflect a certain optimism on the part of the investigators. Although the study was blinded, both arms were receiving investigational product and there may have been a desire to minimize reports unflattering to either product.

The following are my conclusions regarding this study:

1. The design is not optimal for answering questions about the impact of the differences between the new and old formulations.
    - Inpatients stabilized on morphine may not be representative of patients coming into treatment
    - The comparison was between induction with buprenorphine/naloxone strips and induction with buprenorphine-only strips (rather than strips vs. tablets)
    - The analysis based on group mean withdrawal scores
        - Patients who dropped out after 1-2 doses of drug during first induction day were excluded from the group analysis.
            - This would exclude any patients with precipitated withdrawal, which occurs at the beginning of dosing.
        - The study not show whether patients on new product are as likely to be able to make the transition from street drugs to a stable dose of buprenorphine as patients on the approved product
2. However, the results were generally not concerning.
    - Two patients in each arm dropped out on first buprenorphine dosing day
    - One *in each arm* had withdrawal scores that were higher after dosing than before (note that all patients are in withdrawal before dosing; this is usual clinical practice intended to prevent precipitation of withdrawal by buprenorphine).

- The others had lower scores or no change.
- This scenario more consistent with patients dropping out due to lack of efficacy (i.e. insufficient relief of withdrawal) than due to precipitated withdrawal.
- COWS scores decreased after dosing for almost all participants. About 60% in each arm had scores that decreased to the mild range after dosing.

7 Review of Safety

Safety Summary

In summary, safety data from approximately 75 patients treated at or above the generally-recommended daily dose for 12 weeks was provided, although virtually none of these used the product at the dose regimen recommended in labeling (a single daily dose of 16 mg/day). Although no major safety concerns were identified, the quality of the main safety study was questionable and data from other studies in the application suggest that this formulation may be more irritating to the oral mucosa than the tablet.

7.1 Methods

- Deaths and SAEs were reviewed across the clinical program.
- Oral mucosal safety review included AEs referable to the mouth across the clinical program, and oral mucosal exams from Studies RB-US-07-0001 and -0002.
- Common AEs were reviewed from Study RB-US-07-0001. Systemic AEs from the clinical pharmacology program were not included because participants were under naltrexone blockade.
- The only lab data reviewed was from Study RB-US-07-0002. Labs were not collected in RB-US-07-0001. Labs from the clinical pharmacology program were not reviewed due to the brevity of exposure, crossover designs, and naltrexone blockade.
- Three specific safety issues (hepatic safety, use in pregnancy, and accidental pediatric exposure) were reviewed by Dr. Elizabeth Kilgore, incorporating post-marketing and literature data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See 5.1

7.1.2 Categorization of Adverse Events

Adverse events in this clinical program were coded using MedDRA. However, because this program was undertaken to provide a way of linking the established adverse event profile of the approved products to the new product, Reckitt Benckiser was asked to do a comparison of the data using COSTART terms, as the original studies and labeling were coded using COSTART.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data was possible because of differences in populations, doses, durations, and study design.

7.2 Adequacy of Safety Assessments

As discussed below, one of the safety concerns emphasized in pre-submission interactions was the issue of local tolerability. Unfortunately, oral mucosal exams performed in Studies RB-US-07-0001 were not performed by dental professionals and it is not clear what credentials or training were required of the personnel performing these examinations. The discrepancy between the number of abnormalities detected in that study and the number of abnormalities detected in the more closely-monitored inpatient study, RB-US-07-0002, cast some doubt on the reliability of the findings in Study -0001. This study also suffered from issues in drug accountability, inexplicable dosing regimens, and lack of adherence to the protocol (one site omitted Visit 2, one site conducted study visits at a different interval than specified, subjects who did not meet criteria were enrolled) casting doubt on the sensitivity of this study in identifying anything but the most obvious safety signals.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Only Study RB-US-07-0001 provides data on exposures exceeding a few days. The dose-by-duration table below, prepared by Reckitt Benckiser at Agency request, illustrates the cumulative exposure to the experimental product. This shows that there are 126 patients exposed for 12 weeks at any dose. Considering only those using the product in the labeled range (generally 12 mg-16 mg), there appear to be fewer than 80 patients contributing three months of safety data. Also, as discussed more thoroughly in the review of the individual study, virtually none of the patients took their medication as recommended in the labeling, as a single daily dose. Furthermore, although 12 mg/3 mg and 16 mg/4 mg strips were available for the clinical trial, they are not proposed for marketing. The currently-marketed product, Suboxone tablets, is available only in 2 mg/0.5 mg and 8 mg/2 mg formulations, so that patients taking the labeled dose of 16 mg/day are to use two tablets simultaneously, as was done in the clinical trial supporting approval of the tablet. In the film strip study, however, patients using a single daily dose of 16 mg were provided with 16 mg strips (although drug dispensing data shows some switching back and forth between 16 mg strips and twice the number of 8 mg strips for certain subjects), so there is very little, if any, data on using the film strip product as recommended in labeling, namely, two 8 mg strips sublingually used simultaneously. (b) (4) Therefore, experience with the 16 mg strip may provide some support for use of the 2 x 8 mg regimen.

Table 14.6.1.11 Cumulative Time on Dose by Dose Level in Study RB-US-07-0001
(Safety Set)

Treatment: Suboxone [redacted] Sublingual (N=194)

Dose Buprenorphine/Naloxone(mg)	Number of weeks on dose											
	1	2	3	4	5	6	7	8	9	10	11	12
At least 2	179	176	176	164	164	158	158	152	152	141	139	126
At least 4	177	174	174	162	162	158	158	152	152	141	139	126
At least 6	168	165	165	153	153	149	149	143	143	131	128	118
At least 8	163	161	160	149	149	145	145	139	138	126	124	114
At least 10	118	117	117	107	104	100	98	93	93	85	83	77
At least 12	115	114	113	104	102	99	98	93	93	85	83	77
At least 16	109	108	107	100	99	96	95	90	90	82	80	74
At least 17	63	63	61	56	56	47	45	39	39	36	35	31
At least 18	62	62	61	56	56	47	45	39	39	36	35	31
At least 20	62	62	61	56	56	47	45	39	39	36	35	31
At least 24	61	61	60	56	56	47	45	39	39	36	35	31
At least 28	14	14	12	10	10	8	8	6	6	4	4	3
At least 32 or more	14	14	12	9	9	7	7	5	5	4	4	3

7.2.2 Explorations for Dose Response

Not done.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Only adverse events and oral mucosal exams were included in the safety study, RB-US-07-0001.

EKGs and labs were included at baseline and exit in study RB-US-07-0002.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new data submitted.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the development program for this product.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported in Study RB-US-07-0002.

Six SAEs were reported in Study RB-US-07-0001 and one in the clinical pharmacology program. Of these, several were clearly unrelated to study drug (all were assessed as unrelated by the sponsor). The table below briefly lists the events and my assessment of relatedness. Events from both the sublingual group and the buccal group for Study RB-US-07-0001 are included in this presentation for completeness.

One of the events is suggestive of precipitated withdrawal, and may therefore be related to the enhanced bioavailability of the naloxone component in the new formulation.

Patient	Event	Comment
Sublingual		
333010 35 yo F	Injuries sustained as a passenger in an MVA	Unrelated
333073 32 yo F	Cervical cancer dx after ~2 months on study drug	Unrelated
333233 31 yo M	Kidney stones in pt w/previous h/o kidney stones, dx after ~5 wks on study drug	Unrelated
333149 49 yo M	Nausea, chest pain, vasovagal syncope w/injury during initiation of study drug treatment at high dose	Possibly related
Buccal		
111011 37 yo M	MVA, no details, ~wk 5 of study drug	Cannot assess
111047 30 yo M	Esophageal cancer dx ~wk 6 of study drug	Unrelated
Crossover (clinical pharmacology)		
630 38 yo M	Acute optic neuritis on the day of dosing with 4 mg Subutex tablet. Had received 4 mg buprenorphine soluble film sublingually 2 wks prior and buccally 4 weeks prior	Cannot assess

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Clinical Pharmacology Program

In the clinical pharmacology program, there appear to have been two modes of recording whether or not a discontinuation was due to an adverse event, an "AE form" and a "reason for discontinuation" field on the CRF. Additionally, Reckitt Benckiser did not identify what treatment was administered associated with the discontinuation due to AE, noting that "Because of the crossover nature of the studies, summaries represent subjects according to the treatment of the first period of the study." Therefore, it is not possible to determine whether any of the treatment arms (buprenorphine strips, Suboxone strips, Subutex tablets, Suboxone tablets) was more likely to lead to discontinuation due to adverse events. Overall, 2-3% of participants discontinued due to AEs.

	All treatments N - 822
Discontinued due to AE per AE form	19 (2%)
Discontinued due to Adverse Event (per "reason for discontinuation")	25 (3%)

Inspection of the submitted narratives suggest that most patients who discontinued did so because of nausea and vomiting. These symptoms may be caused by naltrexone given prior to the test article.

7.3.3.2 Study RB-US-07-0001

Ascertainment of dropouts due to adverse events in the clinical program was complicated by the unusual design of the case report form for Study RB-US-07-0001. The case report form did not give "adverse event" as an option for indicating the reason for study discontinuation. This was intended to be written in as a choice next to "other."

Conversely, administrative documents not part of the case report form (a "tracking sheet") included a check box for reason for study discontinuation and did give "adverse event" as an option.

At FDA request, RB identified subjects for whom study medication was discontinued due to an adverse event (as recorded in the AE section of the CRF but not in the reason for discontinuation section) and subjects for whom adverse event was listed as a reason for discontinuation on the tracking sheet. A total of 8 discontinuations due to adverse events (2% of participants) were identified. Conflicting study disposition tables based on these different sources are one example of the data quality issues related to this study. Inspection of narratives suggests that several of these cases were not discontinued due to adverse events; however, those that were experienced symptoms consistent with precipitated withdrawal.

Description	Reviewer assessment of relatedness/reason for d/c
Sublingual	
Subject 333010 discontinued because of injuries sustained as a passenger in motor vehicle accident (SAE, see above)	Unrelated
Subject 333049 (Pregnancy; Abortion spontaneous): 31-year-old female began treatment with study drug (16 mg buprenorphine and naloxone soluble film) sublingually on February 27, 2008. On May 14, 2008, the subject reported that she was pregnant *and was discontinued from the study that same day*. (It is not reported whether she was continued on Suboxone tablets or discontinued buprenorphine altogether.) On (b) (6) she had a spontaneous abortion. The sponsor considered this unrelated to study drug. Reviewer assessment is that relatedness cannot be ruled out.	Protocol violation. Adverse event of spontaneous abortion occurred after drug was discontinued; may have been related but was not reason for discontinuation.
Subject (b) (6)/333253 (Pregnancy): 31-year-old female received her first dose of study drug (16 mg buprenorphine and naloxone soluble film) sublingually on March 28, 2008. On May 29, 2008, the subject reported that she had become pregnant. She was discontinued from the study on May 29, 2008 due to the pregnancy, which was considered a protocol violation.	Protocol violation
Subject (b) (6)/333235 (Arthralgia): 39-year-old male received his first dose of study drug (24 mg buprenorphine and naloxone soluble film) sublingually on March 24, 2008. On June 11, 2008, the subject experienced worsening of left knee pain. The sponsor indicates in the submission that this subject was permanently discontinued on June 13, 2008 due to the event of arthralgia. However, the case report form indicates that the patient was discontinued due to a protocol violation, because he was taking Percocet and Oxycontin, evidently related to knee pain, which was not recorded as an AE at the time but added as a site-generated clarification later on.	Protocol violation
Subject 333129 (~~Vision blurred~~; Constipation; Poisoning; Disturbance in attention; Headache; Insomnia; Withdrawal syndrome; Hyperhidrosis): 39-year-old male was randomized to sublingual treatment on February 29, 2008 and was provided 20 film strips (dose not specified in CRF). The CRF indicates that the patient reported on March 7 that on the first day of dosing, he experienced "headache, intoxication, decreased mental clarity, loss of focus, worsening withdrawal syndrome, constipation, insomnia, and sweating." He discontinued study drug although it is not clear when; only 9 of the 20 film strips were returned. Note that the MedDRA code "vision blurred" appears to be erroneous; in context the term "loss of focus" does not appear to refer to visual acuity.	D/C due to adverse events; description consistent with withdrawal.

Buccal	
Subject (b) (6)/111011 (Road traffic accident): This subject was described has having discontinued because of an SAE; however the detail regarding the SAE suggests the subject was lost to follow-up.	Lost to f/u
Subject (b) (6)/111047 (Oesophageal carcinoma): This subject voluntarily withdrew consent because of an SAE (see above)	Unrelated
Subject (b) (6)/333222 (Nausea; Back pain; Migraine; Somnolence): 38-year-old male received his first dose of study drug (16 mg buprenorphine and naloxone soluble film) buccally on March 19, 2008. On March 21, 2008, the subject experienced symptoms which he described in the dose preference questionnaire as "gave me extreme [sic] headaches, sick, moore [sic] back pain." These complaints were coded as "nausea, back pain, migraine, and somnolence," (although the CRF originally said "withdrawal") all which were considered to be moderate in severity and probably related to study drug. Apparently the subject continued on drug until March 29th but then withdrew his consent to participate in the study on March 31, 2008 because of these events.	D/C due to adverse events; description consistent with withdrawal.

7.3.3.3 Study RB-US-07-0002

Four participants discontinued prematurely. Although all four discontinued in the context of withdrawal symptoms shortly after initiation of sublingual film administration, the two in the buprenorphine film arm were characterized as dropouts due to adverse events, while the two in the Suboxone film arm were characterized as participant request.

Subject ID 112: 44-year-old white female, withdrew from the study after receiving two doses of 4 mg (2 x 2/0.5 mg) sublingual buprenorphine/naloxone soluble films at 09:02 and 11:00 on 30 April 2008. Her last dose of morphine was at about noontime on 29 April 2008, the day before starting soluble film administration. Prior to administration of soluble films, she was already experiencing withdrawal symptoms including nausea, abdominal pain, vomiting, and piloerection (moderate severity). Anxiety was noted on the COWS. Her COWS score was 17 before films were administered and 19 one hour afterwards. (Her peak score after the naloxone challenge had been 29.) She was released after requesting to withdraw from the study due to her uncomfortable withdrawal symptoms. This discontinuation was characterized as "subject request."

Subject ID 113: 53-year-old African-American male, withdrew from the study after receiving two doses of 4 mg (2 x 2 mg) sublingual buprenorphine soluble films at 09:02 and 12:15 on 30 April 2008. His last dose of morphine was about noontime on 29 April 2008, the day before starting soluble film administration. Prior to administration of soluble films, he was already experiencing withdrawal symptoms including moderate nausea, chest pain, and chills. These

symptoms continued after soluble film administration and he experienced the start of moderate vomiting. His COWS score was 13 prior to film administration and 17 one hour afterward. (His peak score during naloxone challenge was 6). He was released from unit the following day 1 May 2008 "due to AEs experienced during withdrawal."

Subject ID 137: 38-year-old white female, withdrew from the study after receiving two doses of 4 mg (2 x 2/0.5 mg) sublingual buprenorphine/naloxone soluble films at 09:07 and 11:08 on 23 June 2008. Her last dose of morphine was about noontime on 22 June 2008, the day before starting soluble film administration. Prior to administration of soluble films, she was already experiencing withdrawal symptoms including moderate indigestion, piloerection, anxiety, and irritability. Her COWS score was 13 prior to soluble film administration and 3 one hour afterward. (Her peak score during naloxone challenge had been 8.) She was released on 23 June 2008 after requesting to withdraw from the study, noting that the study medication didnot sufficiently ease her withdrawal symptoms and also claiming a family medical emergency. This discontinuation was characterized as "subject request."

Subject ID 141: 21-year-old white female withdrew from the study after receiving one dose of 4 mg (2 x 2 mg) sublingual buprenorphine soluble films at 08:55 on 27 June 2008. Her last dose of morphine was about noontime on 26 June 2008, the day before starting soluble film administration. Prior to administration of soluble films, she was already experiencing withdrawal symptoms including moderate anxiety, stomach discomfort, arthralgia, cold sweat, rhinorrhea, irritability, lacrimation, restlessness, yawning, and tachycardia. These continued after soluble film administration and tremor (moderate in severity) was noted. Her COWS score was 15 prior to film administration and unchanged one hour later. Her peak score during naloxone challenge had been 18. She was released from the RRF on 27 June 2008, "based on her decision" due to AEs experienced during withdrawal . This discontinuation was characterized as being due to "adverse event."

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Oral Mucosal Tolerability

Local mucosal effects of the strip formulation were identified as a key safety concern for this review. In summary, the main safety study conducted to address this concern identified no particular treatment-emergent safety issues related to the mouth, but data from both the clinical pharmacology program and a the small, inpatient, induction study suggest that the strip formulation may be associated with treatment-emergent oral complaints, although none would be considered serious. The data from the clinical pharmacology program suggest that the filmstrip formulation may be more irritating than the tablet. For a variety of reasons, the data from the large safety study are not convincing.

Notably, there are no AERS reports associated with Suboxone coded to HLGT Oral Soft Tissue Conditions[3]

[3] Search performed by Dr. Afrouz Nayernamaa 6/5/09

7.3.5.1.1 Oral Exams

Specific exams of oral mucosa were conducted only in Studies RB-US-07-001 and RB-US-07-002.

7.3.5.1.1.1 Study RB-US-07-0001

Study RB-US-07-001 was conducted primarily to identify any new safety concerns related to the delivery of the buprenorphine/naloxone combination in a new dosage form, a soluble filmstrip for transmucosal delivery. No products using this type of delivery system are marketed, although the technology is similar to the strips used for oral delivery of cough/cold products and breath fresheners. Special attention was given to evidence of local oral irritation.

Oral exams were conducted at each visit, albeit not by dental professionals or others specifically qualified to evaluate the oral mucosa. It is likely that only the most obvious and dramatic of oral mucosal abnormalities would have been detected in this way. The protocol stipulated that any abnormal findings were to be recorded both as an oral exam score but also as an adverse event, however, this appears to have been done inconsistently.

Overall, 10 of the 194 subjects randomized to treatment with sublingual study drug had either a treatment-emergent abnormal exam recorded, or a spontaneous adverse event referable to the mouth/tongue/oral mucosa. No patient had both.

According to Reckitt Benckiser, 121 subjects completed an oral mucosa exam at visit 10 and at all previous visits. (Because Visits 1 and 2 were combined at one study site, this represented 9 mucosal exams many subjects.) Review of the submitted datasets located 9 or 10 exam results for 120 (not 121) subjects.

The overwhelming majority of the oral exams were graded as “0” (normal mucosa).
Only 6 study participants treated with sublingual study drug had an abnormal exam at any time during the study. One additional patient (333073) has an adverse event of “oral mucosal exam=grade 1 abnormality” recorded in the AE dataset but no abnormal exam recorded in the Oral Exam dataset.

In summary, these exams provided little evidence of treatment-emergent mucosal abnormalities, but may have lacked sensitivity due to the lack of training of the examiners. Furthermore, as will be discussed below, the dosing regimen employed by the vast majority of subjects differs substantially from the recommended dosing regimen in the label. Specifically, almost no patients were using a single daily dose of study drug; therefore the data represent findings collected in the setting of patients using small, divided doses rather than the specific doses in labeling. Indeed, because a 16 mg strip was provided for the study but is not proposed for marketing, it is unlikely that any patient would have been treated with two 8 mg strips simultaneously, as recommended in the labeling as the target dose for all patients. Therefore, although no concerning findings were generated in this study, it may provide little reassurance about the product when used according to the proposed labeling.

7.3.5.1.1.2 Study RB-US-07-0002

In this study, an oral mucosal examination was performed at baseline and at discharge from the residential unit to determine if the soluble film caused any irritation of the mucosa. Baseline abnormalities (localized mucosal erythema and/or irritation without ulceration, assessed as Grade 1 severity) were common at baseline. Seven of the 38 study participants who were randomized to treatment (18%) had abnormalities at baseline. In addition, of the fifteen subjects listed as "not treated" (subjects discontinued during morphine stabilization phase prior to administration of film strip), six (40%) had baseline Grade 1 abnormalities. This is an overall rate of baseline abnormalities in 25% of those admitted to the research unit, in contrast to the very low rate of abnormalities observed in study RB-US-07-0001.

After four days of film strip treatment, four subjects, one in each arm, had abnormalities at discharge which were not present at baseline, including one subject described as having developed "blisters on gums" on the last day of buprenorphine film strip administration. The Ns in the table below represent the patients in the sponsor's "evaluable" population.

	Buprenorphine strips N = 19	Buprenorphine/naloxone strips N = 16
Treatment-emergent mucosal abnormalities	2 (11%)	2 (13%)

It is notable that the rate of both baseline and treatment-emergent mucosal abnormalities was much higher in this carefully-monitored population than in the population that participated in the safety study. Note that the duration of treatment with the film strip products in this study was only four days.

The more careful monitoring in this study identified as surprisingly higher rate of mucosal abnormalities, both at baseline and emerging during treatment. This further underscores the concern that the main safety trial lacked sensitivity to identify local oral effects of the study drug.

7.3.5.1.2 Adverse Events Related to the Mouth

7.3.5.1.2.1 Study RB-US-07-0001

A string search in the verbatim term field and the MedDRA LLT field for "mouth," "oral," "gum," "ging," "gloss," "oral," and "tongue" was used to supplement the HLGT "Oral Soft Tissue Conditions." Using this method, nine patients reporting events referable to the mouth, tongue, and oral mucosa were identified. These included three patients for whom the AE was an oral exam abnormality and six for whom the AE was a spontaneously-reported AE. Notably, there were no spontaneous complaints from the three subjects with oral mucosal abnormalities on exam. In addition, there were two patients for whom oral mucosal exam abnormalities were recorded in the Oral Exam database who were not listed in the AE dataset. Notably, these two patients also had no spontaneously-reported oral complaints.

Complaints reported spontaneously included:

Preferred Term	# of Patients
GLOSSODYNIA (includes verbatim terms burning of tongue, burning tip of tongue, tongue tender)	3
HYPOAESTHESIA ORAL (includes verbatim term numbness tongue)	2
TONGUE COATED	1

7.3.5.1.2.2 Study RB-US-07-0002

Only one adverse event referable to the oral mucosa was reported; this was the above-mentioned patient with gingival blisters.

7.3.5.1.2.3 Clinical Pharmacology Program

Reckitt Benckiser identified the following adverse events related to the oral mucosa in the clinical pharmacology program. The Ns represent the number of subjects participating in that arm of the study. Most studies had crossover design and subjects could have received more than one treatment. Events were grouped according to the treatment period in which they occurred[4]. Not enough information is provided to determine whether the cases coded as "herpes" were actually viral eruptions vs. some other time of mouth sore that could potentially be drug-related. (One case had lower level term of "cold sore.") However, even with these events excluded it appears that the strip formulations are more likely than the tablet formulations to be associated with complaints referable to the mouth. This population also, obviously, reported far more oral adverse events than did the participants in Study RB-US-07-0001.

[4] The CRF did not have this information, and it had to be calculated by Reckitt Benckiser based on the date of the event.

"Special interest" Adverse Events in Clinical Pharmacology Program

	Subutex		Buprenorphine Soluble Film (N=351)		Suboxone		Suboxone (b) (4)	
Preferred Term	(N=206)				(N=313)		(N=459)	
At Least One Special Interest Adverse Event	2	1%	13	4%	8	3%	31	7%
PARAESTHESIA ORAL	1	0.5%	7	2%	2	1%	6	1%
DYSGEUSIA	1	0.5%	1	0.3%	3	1%	4	1%
TOOTHACHE	0		2	1%	2	1%	1	0.2%
ORAL HERPES	0		0		0		4	1%
HYPOAESTHESIA ORAL	0		1	0.3%	0		2	0.4%
SALIVARY HYPERSECRETION	0		0		0		2	0.4%
APHTHOUS STOMATITIS	0		0		1	0.3%	0	
CHEILITIS	0		0		0		1	0.2%
GINGIVITIS	0		0		0		1	0.2%
ORAL PAIN	0		1	0.3%	0		0	
SALIVA ALTERED	0		1	0.3%	0		0	

Table adapted from Table 14.7.14.1 in 4-month Safety Update

These data again cast doubt on the seemingly reassuring findings of the main safety study.

7.3.5.2 Hepatic Safety

See Dr. Elizabeth Kilgore's review of specific safety concerns for a comprehensive review of hepatic safety issues.

7.3.5.3 Precipitation of Withdrawal

As noted above in discussion of discontinuations due to adverse events, two participants in Study RB-US-07-0001 and four participants in Study RB-US-07-0002 discontinued prematurely in association with symptoms consistent with withdrawal. Although the patients in RB-US-07-0002 were in acute withdrawal due to the design of the study, and may have been experiencing inadequate treatment of withdrawal (i.e., lack of efficacy, rather than and adverse effect of the drug), in theory, the participants in RB-US-07-0001 should have been stabilized patients, not using illicit drugs, and having no reason to experience withdrawal symptoms. In addition, one patient in RB-US-07-0001 who ultimately went on to complete the study had AEs of nausea and vomiting shortly after treatment initiation, which could be attributed to withdrawal.

These three cases, described again below, are suggestive of precipitated withdrawal, which is difficult to explain in patients already stabilized on buprenorphine.

Subject 333129 39-year-old male was randomized to sublingual treatment on February 29, 2008 and was provided 20 film strips (dose not specified in CRF). The CRF indicates that the patient reported on March 7 that on the first day of dosing, he experienced "headache, intoxication, decreased mental clarity, loss of focus, worsening withdrawal syndrome, constipation, insomnia, and sweating." He discontinued study drug although it is not clear when; only 9 of the 20 film strips were returned.

Subject 333222 38-year-old male received his first dose of study drug (16 mg buprenorphine and naloxone soluble film) buccally on March 19, 2008. On March 21, 2008, the subject experienced symptoms which he described in the dose preference questionnaire as "gave me extreme [sic] headaches, sick, moore [sic] back pain." These complaints were coded as "nausea, back pain, migraine, and somnolence," (although the CRF originally said "withdrawal") all which were considered to be moderate in severity and probably related to study drug. Apparently the subject continued on drug until March 29th but then withdrew his consent to participate in the study on March 31, 2008 because of these events.

Subject 333149 49 yo M received his first dose of study drug (32 mg buprenorphine and naloxone soluble film) sublingually on 3 March 2008. On 4 March 2008, the subject reported vomiting, which was classified as severe in intensity. On 6 March 2008, the subject experienced nausea, chest pain, and vasovagal syncope, during which he fell and lacerated his left ear. Although the sponsor classified this event as unrelated to study drug, all the reported symptoms could conceivably be related to withdrawal, as the subject was receiving a cumulative dose of 8 mg naloxone and may have experienced precipitated withdrawal. Ultimately, the subject completed the study, receiving a fnal dose of study drug on 27 May 2008

7.3.5.4 Study Drug Accountability/Diversion

The protocol for the only outpatient study, Study RB-US-07-0001, called for dispensing approximately three extra days' supply of study drug at each visit to account for variations in scheduling. Unused drug was to be collected at each visit and a "percent compliance" calculated based on the amount returned. In the dataset for drug accountability, this variable is blank for 1707/2497 (68%) rows, because there is no record of the study drug returned, suggesting that there was poor attention to this aspect of the protocol. In the 32% of visits for which there is a "percent compliance" recorded, it is over 100% in 28% of cases, indicating that subjects failed to return excess study drug supply. Taken together with multiple reports of lost or stolen study drug, or missing empty packets, this suggests that there may have been significant diversion of study drug supply. Although there is no definite evidence that this is the case, there is certainly nothing in this data to support the contention that this product would be *less* prone to diversion than tablets dispensed in bottles. Reckitt suggests that the inability to "cheek" this formulation could prevent diversion; however this would only be applicable in the case of supervised administration.

A search of the protocol deviation dataset using terms such as *lost, stolen, packet, strips, failed, return, missing* yielded several hundred listings which were inspected to remove events unrelated to study drug accountability. This yielded 294 events reported in 155 different patients (all at site 333, where total enrollment was 233) in which empty packets were not returned, unused study drug was not returned as required, or study drug was reported lost, stolen, or destroyed. About half of the patients had one such report but two or three reports by the same patient were common, and 6 patients had as many as 6-7 such violations. No action appears to have been taken by the study site.

Only Site 333 reported these events as protocol deviations. At Agency request, Reckitt Benckiser provided (in line listing form only, not a dataset amenable to analysis) a listing of

patients with similar deviations at the other two sites. This revealed 18 (of 27 enrolled) patients at Site 777 with "missing" study drug supply (none "lost" or "stolen") and 118 (of 122 enrolled) patients at Site 111 with missing, stolen, or lost drug supply. Most of these patients are listed as having "missing" packets on only a single occasion; however, some are missing substantial quantities of packets (up to 377 packets at one visit), and some patients reported "stolen" or "lost" unused drug supplies on more than a single occasion.

At Agency request, Reckitt Benckiser provided a tabulation showing how many strips of each dosage strength were "prescribed" to patients (i.e., the amount the patient was instructed to use), how many were "dispensed" (patients were to get either a one- or two-week supply of medication, plus an additional three-day supply) and how many strips were returned, calculating the number of strips which were unaccounted for. In this tabulation, if a patient were dispensed medication and he/she did not return to the clinic prior to Visit 9 (or at all), the amount prescribed was considered to be zero, which elevates the calculation of the amount of drug considered to be "missing." Overall, 12,900 strips were provided to participants in excess of the amount prescribed. Of these, 5918 (46%) were not returned. Across sites the amount of missing study drug ranged from 38% of the strips due to be returned at Site 333 to 90% of the strips due to be returned at Site 777. The table below, constructed by the reviewer from the data submitted, illustrates the substantial quantity of drug supply unaccounted for.

Site	Dose	# of (b) (4) Dispensed	# of (b) (4) Prescribed	# of (b) (4) Returned	# of (b) (4) Expected to be Returned	# of (b) (4) Missing	% of Expected Returns Not Returned
111	2 mg	8,674	6753	1162	1,921	759	40%
	8 mg	6862	5411	773	1,451	678	47%
	12 mg	173	97	35	76	41	54%
	16 mg	207	155	33	52	19	37%
	total	15,916	12,416	2,003	3,500	1,497	43%
333	2 mg	3020	2412	459	608	149	25%
	8 mg	13687	10621	2053	3,066	1,013	33%
	12 mg	11490	9283	1221	2,207	986	45%
	16 mg	8917	7086	1080	1,831	751	41%
	total	37114	29402	4813	7712	2899	38%
777	2 mg	3213	2513	86	700	614	88%
	8 mg	4210	3338	59	872	813	93%
	12 mg	146	112	0	34	34	100%
	16 mg	448	366	21	82	61	74%
	total	8017	6329	166	1688	1522	90%
All	2 mg	14,907	11,678	1,707	3,229	1,522	47%
	8 mg	24,759	19,370	2,885	5,389	2,504	46%
	12 mg	11,809	9,492	1,256	2,317	1,061	46%
	16 mg	9,572	7,607	1,134	1,965	831	42%
	total	61,047	48,147	6,982	12,900	5,918	46%

No information on accountability of drug supply for the tablet formulation is available, because the registration studies were done under supervised administration conditions (and in some cases used a liquid formulation). Therefore, there is no basis for comparison but there does not appear to be any reason to conclude that this formulation rendered the study drug particularly resistant to diversion.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The clinical pharmacology program was conducted in subjects under naltrexone blockade and does not reflect the adverse event profile in the intended population. Study RB-US-07-0002 involved only five days of dosing with the experimental drug and appears to have recorded as adverse events all symptoms of withdrawal identified by administration of the COWS; accordingly, AEs are reported for essentially the entire study population and provide little meaningful information about the safety profile of Suboxone strip. Therefore only the AE dataset for Study RB-US-07-0001 was considered in the review of common AEs.

Adverse events reported in Study RB-US-07-001 were collected by spontaneous report at study visits and coded using MedDRA. However, to facilitate comparison to the existing safety experience with the approved sublingual tablets and solution, the MedDRA terms were mapped to corresponding COSTART terms. The tables below illustrate the COSTART-coded common adverse events in Study RB-US-07-0001. Compared to the pivotal studies included in the approved labeling for Suboxone and Subutex, there was a substantially lower rate of adverse events reported. This may relate to the difference in population (stabilized at least 30 days vs. new entrants to treatment) or may reflect the overall cavalier conduct of Study RB-US-07-0001.

Adverse Events reported in at least 2% of participants, by COSTART Body System and Preferred Term in Study RB-US-07-001

Body System/Adverse Event (COSTART Terminology)	Sublingual N=194 n (%)	Buccal N=188 n (%)	Total N=382 n (%)
At least one adverse event	54 (27.8%)	62 (33.0%)	116 (30.4%)
Body as a Whole	29 (14.9%)	34 (18.1%)	63 (16.5%)
Pain	8 (4.1%)	7 (3.7%)	15 (3.9%)
Accidental injury	5 (2.6%)	9 (4.8%)	14 (3.7%)
Infection	6 (3.1%)	7 (3.7%)	13 (3.4%)
Headache	2 (1.0%)	4 (2.1%)	6 (1.6%)
Skin and Appendages	7 (3.6%)	6 (3.2%)	13 (3.4%)
Rash	2 (1.0%)	6 (3.2%)	8 (2.1%)
Respiratory System	6 (3.1%)	5 (2.7%)	11 (2.9%)
Sinusitis	3 (1.5%)	4 (2.1%)	7 (1.8%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.
Data derived from: Clinical Study Report for RB-US-07-0001, Statistical Table 13.1.2.

For comparison, the AE tables from the approved labeling are shown below.

Adverse Events (≥ 5%) by Body System and Treatment Group in a 4-week Study

	N (%)	N (%)	N (%)
Body System /Adverse Event (COSTART Terminology)	**SUBOXONE 16 mg/day N = 107**	**SUBUTEX 16 mg/day N = 103**	**Placebo N = 107**
Body As A Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. The table below shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

Table 4. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study*Body System /Adverse Event* **(COSTART Terminology)**	*Buprenorphine Dose**				
	Very Low* **(N=184)**	**Low* (N=180)**	**Moderate* (N=186)**	**High* (N=181)**	**Total* (N=731)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**

Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
"Very low" dose (1mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8mg solution) approximates a 12 mg tablet dose
"High" dose (16mg solution) approximates a 24 mg tablet dose

Reckitt Benckiser proposes to include (b) (4)

(b) (4)

with other formulations, and, if anything, may be more irritating locally.

7.4.2 Laboratory Findings

Clinical laboratory were not collected in Study RB-US-07-0001. Study RB-US-07-0002 included laboratory assessments at admission and discharge (a maximum of 5 days of exposure to buprenorphine). Hepatic enzymes increased during the brief period of treatment in this study. Other analytes did not show notable changes from baseline.

See Dr. Elizabeth Kilgore's review of specific safety issues for further discussion of the hepatic enzyme data.

7.4.3 Vital Signs

Vital signs were not collected in Study RB-US-07-0001. Vital sign data from RB-US-07-0002 reflects patients in acute withdrawal and provides little meaningful information.

7.4.4 Electrocardiograms (ECGs)

No new ECG data was reviewed.

8. Postmarketing Experience

Postmarketing safety information on buprenorphine is derived from reports on its use as an analgesic as well as its use as a treatment for opiate dependence.

As an analgesic, buprenorphine is marketed by Reckitt Benckiser as a sterile injection (0.3 mg/ml) and sublingual tablets (0.2 mg and 0.4 mg) under proprietary names Buprenex, Buprex, and Lepetan, and by Otsuka Pharmaceuticals as a suppository under the proprietary name Lepetan. The parenteral product is marketed in 37 countries and the tablets in 36 countries. Products have been discontinued from marketing in 16 countries.

Subutex and Suboxone tablets for treatment of opioid dependence have been approved in 46 and 43 countries, respectively and launched in 31 and 27 countries respectively.

Appendix 9.4 illustrates the worldwide marketing status as of March, 2009.

Reckitt Benckiser reports that

For Subutex and Suboxone SL tablets, total postmarketing exposure data from 2001 (Subutex) or from 2003 (Suboxone) through April 30, 2008 are available from 27 countries. Data prior to 2001 are no longer available on Reckitt Benckiser's computer network. Subutex SL tablets are also available in other countries (such as Cyprus, Malta, Luxembourg, etc.); however, postmarketing exposure data from those countries are not available. Postmarketing exposure data from buprenorphine products marketed by Schering-Plough and Otsuka are not included[5]

During the period between 2001 and April 30, 2008, (b) (4) of Subutex were distributed in 27 countries. Assuming an average daily dose of 8 mg Subutex, this is equivalent to (b) (4) million daily doses, or 1.08 million patient-years of exposure. During the period between 2003 and April 30, 2008, (b) (4) of Suboxone were distributed in 27 countries. Assuming an average daily dose of 8 mg Suboxone, this is equivalent to (b) (4) daily doses, or 474,455 patient-years of exposure. During the period between March 2003 and April 30, 2008 (b) (4) of Subutex were distributed in the United States. Assuming an average daily dose of 8 mg Subutex, this is equivalent to (b) (4) daily doses, or 51,886 patient-years of exposure. During the period between January 2003 and April 30, 2008, (b) (4)) of Suboxone were distributed in the United States. Assuming an average daily dose of 8 mg Suboxone, this is equivalent to (b) (4) daily doses, or 439,682 patient-years of exposure.

The tables below, from Reckitt Benckiser's Summary of Clinical Safety (2.7.4, Page 106 and 113) illustrate the most frequently-reported adverse events (i.e., ≥1% of total events) since 1997 and the number of these events during the period from January 1, 2008 to April 30, 2008, the time span of their last periodic safety report.

[5] Schering Plough, not Reckitt Benckiser, markets buprenorphine products throughout most of the world. The sales figures and adverse events provided are from Reckitt Benckiser.

Most Frequently-Reported Adverse Events Associated with Subutex (b) (4) Tablets

Preferred Term	1/1/2008-4/30/2008	Total since 1/1/1997
Drug exposure during pregnancy	241	865
No adverse drug effect / No adverse effect / No adverse event / No adverse reaction	170**	464
Drug abuse / Drug abuser / Incorrect route of drug administration / Intentional drug misuse / Intentional misuse	23	372
Drug withdrawal syndrome / Withdrawal syndrome	50	279
Drug withdrawal syndrome neonatal	16	148
Vomiting	13	121
Nausea	24	115
Hyperhidrosis	7	97
Anxiety / Feeling jittery / Nervousness	32	96
Edema / Edema peripheral / Gravitational edema	7	95
Headache	13	92
Rash / Rash erythematous / Rash generalized / Rash macular / Rash maculo-papular / Rash pruritic / Rash pustular / Urticaria / Urticaria chronic	9	88
Alanine aminotransferase / Alanine aminotransferase increased / Aspartate aminotransferase increased / Gamma-glutamyltransferase abnormal / Gamma-glutamyltransferase increased / Hepatic enzymes increased / Liver function test abnormal	2	80
Abscess / Abscess bacterial / Abscess limb / Injection site abscess / Muscle abscess / Staphylococcal abscess / Streptococcal abscess / Subcutaneous abscess	6	76

* Number of reports of individual event is ≥1% of the total number of adverse events reported from January 1, 1997 through April 30, 2008. No postmarketing events were reported for Subutex prior to 1997.

** Two 'no adverse effect' events were due to drug overdose, all others were due to exposure during pregnancy (maternal).

Most Frequently-Reported Adverse Events Associated with Suboxone (b) (4) Tablets

Preferred Term	1/1/2008-4/30/2008	Total since 1/1/2003
Drug exposure during pregnancy	230	414
Nausea	76	404
Vomiting / Vomiting projectile	43	313
Drug withdrawal syndrome / Withdrawal syndrome	124	310
No adverse effect / No adverse event / No adverse reaction	185**	294
Hyperhidrosis	42	246
Headache	60	233
Anxiety / Feeling jittery / Nervousness	45	217
Insomnia	45	197
Asthenia / Fatigue	42	165
Diarrhea	12	145
Chills	7	137
Edema / Edema peripheral / Generalized edema / Gravitational edema / Pitting edema	38	128
Rash / Rash erythematous / Rash generalized / Rash macular / Rash maculo-papular / Rash pruritic / Rash pustular / Urticaria	21	113
Muscle contractions involuntary / Muscle spasms / Muscle spasticity	16	108
Abdominal pain / Abdominal pain upper / Gastrointestinal pain	8	100
Dizziness	20	98
Tremor	18	98
Pain	15	91
Somnolence	15	88
Depression / Depressed mood	23	77
Constipation	17	74
Pruritus / Pruritus generalized	18	73
Drug abuse / Drug abuser / Incorrect route of drug administration / Intentional drug misuse / Intentional misuse	9	73

* Number of reports of individual event is ≥1% of the total number of adverse events reported from January 1, 2003 through April 30, 2008.

** One 'no adverse effect' event was due to exposure in breast milk, one to intentional misuse (i.e., swallowed SL tablet), and one to use by an opiate-naïve individual. All others were due to exposure during pregnancy (maternal) except for one event which was due to parental exposure (i.e., buprenorphine in semen).

Reckitt Benckiser did not provide sales figures for buprenorphine analgesic products. A table was provided summarizing AEs from 3/31/05 through the present (it is not clear why this window was chosen, as the products have been available for over 25 years) and for the last periodic reporting period. Notably, the types of reports is similar for both the analgesics and the dependence treatment formulations. This may reflect, in some cases, off-label use for opioids dependence treatment and/or illicit use.

Most Frequently-Reported Adverse Events Associated with Buprenorphine (Other)

Drug abuser / Incorrect route of drug administration / Intentional drug misuse / Intentional misuse	4	48
Vomiting	5	41
Nausea	9	32
Drug withdrawal syndrome / Withdrawal syndrome	7	31
Drug exposure during pregnancy	5	25
Dependence / Drug dependence	1	24
No adverse drug effect / No adverse effect / No adverse reaction	2**	23
Death / Sudden death	1	21
Dizziness	3	20
Somnolence	2	20
Drug interaction	0	18
Hyperhidrosis	6	17
Confusional state	0	15
Anxiety	5	14
Abscess / Abscess bacterial / Abscess limb / Groin abscess	0	14
Asthenia / Fatigue	0	14
Pruritus / Pruritus generalized	2	13
Insomnia	1	12
Endocarditis / Endocarditis staphylococcal	0	12
Abdominal pain / Abdominal pain upper	1	11
Headache	1	11
Respiratory depression	1	11

* Number of reports of individual event is ≥1% of the total number of adverse events reported from March 31, 2005 through April 30, 2008.

** One 'no adverse effect' event was due to exposure during pregnancy (maternal).

Postmarketing safety information was included in Dr. Kilgore's review of hepatic safety, use in pregnancy, and accidental pediatric exposure.

In addition, Dr. James Kaiser of the Office of Surveillance and Epidemiology examined the AERS database and performed a review of cases relating to hepatic injury.

9 Appendices

9. 1 Labeling Recommendations (See my Cross-Disciplinary Team Leader review)

APPEARS THIS WAY ON ORIGINAL

9.2 Detailed Review of Study RB-US-07-0001

A Phase 2 Multi-Center Open-label Study to Assess the Safety and Tolerability of a Buprenorphine/Naloxone Film (b) (4) Administered by the Sublingual and Buccal Routes
Date of first enrollment: 26 February 2008
Date of last subject completed: 21 July 2008

9.2.1 Protocol

9.2.1.1 Objective/Rationale

The purpose of this study was to assess the safety and tolerability on the oral mucosa of buprenorphine/naloxone film strips administered either sublingually or buccally daily for 12 weeks.

9.2.1.2 Overall Design

The study design was an open-label, two-arm study in which approximately 200 subjects who were on a stable regimen of buprenorphine/naloxone sublingual tablet maintenance therapy for a minimum of 30 days immediately prior to study enrollment were to have their buprenorphine/naloxone sublingual tablets replaced with buprenorphine/naloxone film strips daily for 12 weeks, given either sublingually or bucally (100 per group), and were to be followed on an outpatient basis with assessments of local oral mucosa tolerability and safety of the buprenorphine/naloxone film strip.

9.2.1.3 Population and Procedures

9.2.1.3.1 Inclusion/Exclusion Criteria

The protocol called for enrolling up to 400 subjects to ensure at least 100 completers per arm.

The protocol stated that "Subjects will be recruited from the pool of patients being treated at the clinical site for opioid dependence who are on maintenance buprenorphine/naloxone sublingual tablets. Potential candidates may be approached by study staff or respond to advertisements posted in the clinic and will be scheduled to meet with the investigator or designated investigational staff and receive an explanation of the study purpose and requirements."

To be eligible, subjects were required to meet the following criteria:

- Age 18 to 65
- Diagnosis of opioid dependence by medical history according to DSM-IV-TR criteria.
- On a stable dose of 4 to 32 mg daily of Suboxone for at least 30 days.
- Negative pregnancy test during screening and acceptable contraception
- Considered "a suitable candidate" by the investigator

Subjects were to be excluded for:

- Clinically significant abnormal findings on oral cavity exam
- Piercing of the tongue or mouth
- Pregnancy or nursing
- Recent participation in experimental drug or device study

Employees of the study center and their family members were also excluded.

9.2.1.3.2 Procedures

The protocol called for Screening (up to 30 days), Treatment (12-weeks), and Discharge Phases (1 week) of the study. The Screening Phase was to be conducted on an outpatient basis within 30 days prior to the start of treatment. The Treatment Phase consisted of xxxxx visits for study drug dosing and safety, and tolerability assessments. During Week 13, final drug accountability and AE assessments were to be performed and subjects were to be returned to their treatment with Suboxone sublingual tablets. Approximately one week later, they were to return for one final safety visit.

9.2.1.3.2.1 Dosing

Participants were randomly assigned to dosing either sublingually or buccally. Study drug was provided in four different dose levels (note that only two of these are proposed for marketing) and a table was provided explicating how the pre-study dose of Suboxone (which is available only two doses, 2 mg buprenorpine with 0.5 mg of naloxone and 8 mg buprenorphine with 2 mg of naloxone) could be delivered using the available dosages.

Dosing With Study Drug

Dose	*Number of Strips*			
	2/0.5mg strip	**8/2 mg strip**	**12/3 mg strip**	**16/4 mg strip**
4 mg	2			
6 mg	3			
8 mg		1		
10 mg	1	1		
12 mg			1	
14 mg	1		1	
16 mg				1
18 mg	1			1
20 mg		1	1	
22 mg	1	1	1	
24 mg			2	
26 mg	1		2	
28 mg			1	1
30 mg	1		1	1
32 mg				2

The initial protocol stated that no more than three film strips were to be applied at one time to provide the total administered daily dose in the combinations shown in the table, and if more than two film strips were required, the placement of additional strips was to be separated by at least a 5 minute interval. An amendment dated 2/14/08 modified these requirements to "suggestions."

The dose for each subject was to be identical to the individual established daily maintenance dose of Suboxone. The labeling for Suboxone states that "SUBUTEX or SUBOXONE is administered sublingually as a single daily dose in the range of 12 to 16 mg/day." Elsewhere in labeling, physicians are informed that

> The recommended target dose of SUBOXONE is 16 mg/day. Clinical studies have shown that 16mg of SUBUTEX or SUBOXONE is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The dosage of SUBOXONE should be progressively adjusted in increments / decrements of 2mg or 4mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4mg to 24mg per day depending on the individual.

However, for unclear reasons, the protocol indicated that the dose could "range from 4 to 32 mg."[6]

Subjects were randomly assigned to use the study medication either sublingually or buccally, as described below.

Sublingual Administration: For the initial administration, trained staff or the subject were to place the film in the mid portion of the subject's lateral sublingual space; when more than one film was needed, one film was to be placed on each side. If three strips were needed the third strip was to be placed in the mouth at least five minutes after the other two to allow time for the first two strips to dissolve. The subjects will be told not to place more than two sublingual films under the tongue at once.

The subjects were to be told that films should not be chewed or swallowed. Subjects were to be instructed to hold the film in a stationary position, and not to swallow after dosing until the film is completely dissolved or after five minutes.

---

[6] RB provided this explanation at Agency request: "Despite our efforts, we know Suboxone dosages greater than 24/6 mg per day are endorsed through other sources. For example, in TIP 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, it is stated that "Nearly all patients will stabilize on daily doses of 16/4 – 24/6 mg; some, however, may require up to 32/8 mg daily." In another example, BuprenorphineCME.com (supported by ASAM with NIDA funding), which lists itself as an official buprenorphine training program that satisfies the SAMHSA requirement for a DATA 2000 physician waiver (http://www1.buprenorphinecme.com/?id=3030:27868), the maximum recommended buprenorphine dose (for maintenance, after an appropriate induction) is listed as 32 mg/day for patients who are not dependent on opioids, who are dependent on short-acting opioids, or who are dependent on long-acting opioids. Thus, we realize the clinical reality is that daily dosages of Suboxone greater than 24/6 mg per day are being used, and we wanted the protocol to reflect that reality in order to obtain relevant safety information on patients receiving higher daily dosages."

Buccal Administration: For the initial administration, trained staff or the subject were place one film on the inside of the right cheek. As above, both sides were to be used if two strips were administered and five minutes was to elapse before administering a third strip. Instructions were given as above.

9.2.1.3.2.2 Schedule of Visits and Assessments

The following time-and-events table illustrates the planned schedule of assessments:

	Screening	Treatment							Discharge	
Study Week	**Day -30 to -1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**13**	**14**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Informed Consent	X									
Demographics	X									
Medical History	X									
Prior Medications	X									
Oral Mucosa Examination	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen[a]	X	X	X	X	X	X	X	X	X	X
Urine Buprenorphine Screen[b]	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[c]	X			X		X		X	X	
Eligibility Checklist	X	X								
Study Drug Dispensing[d]		X	X	X	X	X	X	X		
Study Drug Accountability[e]			X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X
Prescribe Buprenorphine and Naloxone Sublingual Tablets[f]									X	
Dose Preference Questionnaire									X	

[a] *Per the local study center's standard of care. The Investigator was to determine the subject's continued study participation in the event of a urine drug screen positive for substances other than buprenorphine or naloxone.*
[b] *Point-of-care test.*
[c] *All women.*
[d] *Sufficient buprenorphine and naloxone soluble films were dispensed to be administered daily by the subject until the next visit with an extra three-day supply. The dose and number of study drugs were recorded.*
[e] *The amount and dose of buprenorphine and naloxone soluble films that were not used by the subject since the last dispensing were recorded.*
[f] *Subjects were prescribed a maintenance dose of buprenorphine and naloxone sublingual tablets equivalent to the current dose of soluble film which was adjusted at the discretion of the Investigator.*

9.2.1.3.2.3 Ancillary treatment

All other aspects of the treatment—counseling, urine drug testing, etc.—were to be delivered according to the center's usual care.

9.2.1.4 Evaluations/Endpoints

The study was designed to collect safety data, including adverse events (AEs) and the results of oral mucosal exams.

Any reaction, side effect, or untoward event that occured during the course of the clinical trial, whether or not the event is considered investigational product-related or clinically significant was to be recorded as an AE**.** Clinically significant clinical laboratory abnormalities were also to be recorded as AEs.

Reports of AEs were to be elicited by a verbal probe (e.g., "How are you feeling?") administered starting on Day 1 and at each subsequent study visit. Any events spontaneously reported by the subject or observed by the investigative staff were also to be recorded.

An examination of the oral mucosa for evidence of abnormalities prior to study drug was to be performed by a health care professional (physician, registered nurse, licensed practical nurse, nurse practitioner, or physician's assistant) trained by the Investigator. Six areas (Right Sublingual Area; Left Sublingual Area; Right Upper Buccal Area; Right Lower Buccal Area; Left Upper Buccal Area; Left Lower Buccal Area) were inspected and a severity grade was recorded on the CRF. While all areas were inspected, only a single severity grade was reported according to the scale below.

Severity Grading Scale:
Grade 0: Normal mucosa
Grade 1: Localized mucosal erythema and/or irritation without ulceration
Grade 2: Erythema and/or irritation and induration without ulceration
Grade 3: Ulceration, with or without any other combination of signs

In addition, mucosal AEs were recorded on the AE CRF.

9.2.2 Results

9.2.2.1 Study Conduct/Outcome

9.2.2.1.1 Investigators/Locations

The protocol stipulated that the trial would be conducted as a multi-center study at up to 6 clinical sites. Each site was expected to enroll approximately the same numbers of subjects (approximately 50 per site) at the rate of 10 subjects or more per site per week. As noted above, subjects were to be "recruited from the pool of patients being treated at the clinical site for opioid dependence who are on maintenance buprenorphine/naloxone sublingual tablets."

In practice, only three sites enrolled patients, and only one of the investigators appears (on inspection of the submitted curriculum vitae) to be an addiction treatment physician. One site appears to be a CRO and one site, which enrolled the bulk of the participants, seems to be a general medical clinic. All of the site investigators are, however, listed in the SAMHSA treatment locator database and appear to have the appropriate DEA waivers for buprenorphine treatment. However, it is not clear how a single site would have several hundred patients already in maintenance treatment and available for recruitment. Reckitt Benckiser explained that "All of the principal investigators at the three sites were (and still are) certified to treat 100 patients under DATA. Dr. Sullivan also enrolled patients who were being treated by (b) (4) within the same clinic. These latter two physicians also were (and are) certified to treat 100 patients." Therefore, this site (333) had a potential maximum pool of 300 patients; it remains nevertheless surprising that 233 patients were enrolled at this site as 78% of the entire patient case load at this practice would have had to consent to participate in the trial to achieve this enrollment.

The following investigators/centers were listed in the study protocol.

Site #	Site Investigator	Location	Enrollment (total)	Enrollment (sublingual arm)
111	Boyde J. Harrison, MD	Winston Technology Research, LLC 42110 Highway 195 Haleyville, AL 35565	122	61
333	James Gregory Sullivan, M.D.	Parkway Medical Center 1160 Huffman Road Birmingham, AL 35215	233	119
666 (Also called site 777)	John C. Tanner, DO, FASAM	Beaches Family Medicine 304 16th Avenue North Jacksonville, FL 32250	27	14

9.2.2.1.2 Subject Characteristics.

9.2.2.1.2.1 Subject Disposition

A total of 194 subjects from three study centers were screened and subsequently randomized to treatment with buprenorphine and naloxone soluble film via sublingual administration. (An additional 188 subjects were assigned to treatment by the buccal route. This group does not provide information relevant to the method of use claimed in this application and will generally not be discussed further.)

Of these, 61% were considered "completers." Completers were defined as subjects who completed at least 84 days of buprenorphine and naloxone soluble film therapy, with a clinic visit not more than seven days after last soluble film administration. Some subjects were

considered “non-completers” who are also not listed among those discontinuing prematurely, and some had a completion status of “unknown.” Mean time until discontinuation among subjects treated with buprenorphine and naloxone soluble film administered sublingually and buccally was 61 days.

Subject Disposition is shown in the table below, constructed from the sponsor’s study report.

Randomized	194
Completed[1]	118 (60.8%)
Discontinued any reason[2]	68 (35.1%)
Adverse event	5 (2.6%)
Subject withdrew consent	12 (6.2%)
Investigator decision	8 (4.1%)
Sponsor decision	10 (5.2%)
Protocol violation	2 (1.0%)
Lost to follow-up	17 (8.8%)
Other	19 (9.8%)

[1]Subjects categorized as non-completers and those with missing status are not shown. Thus, the number of subjects completed plus the number discontinued does not equal the number randomized.
[2] Includes subjects with any reason for discontinuation as reported on study case report forms; multiple reasons may have been listed for a given subject.

Notably, the case report form did not give “adverse event” as an option for indicating the reason for study discontinuation. This was intended to be written in as a choice next to “other.”

Conversely, administrative documents not part of the case report form (a “tracking sheet”) included a check box for reason for study discontinuation and did give “adverse event” as an option.

At FDA request, RB identified subjects for whom study medication was permanently discontinued due to an adverse event (as recorded in the AE section of the CRF but not in the reason for discontinuation section) and subjects for whom adverse event was listed as a reason for discontinuation on the tracking sheet. An additional four subjects treated with sublingual study drug were identified who had adverse events requiring discontinuation of study medication.

At Agency request, Reckitt Benckiser provided a tabulation using both sources of information that was used to create the (reviewer-constructed) subject disposition table below. Completers in the table below were defined as subjects who completed at least 84 days of buprenorphine

and naloxone soluble film therapy, with a clinic visit not more than seven days after last soluble film administration.

	N	%
Randomized	194	
Treated (at least one dose)	194	100%
Completed all study visits	125	64%
Statistical Analysis Plan-defined completers[a]	118	61%
Recorded as "discontinued due to an adverse event" on study termination page (not in CRF)	5	3%
AE listed in CRF listed with action "study medication permanently discontinued"	4	2%
Withdrawn from study (CRF)	63	32%
Subject withdrew consent	12	6%
Investigator decision	10	5%
Sponsor decision	8	4%
Protocol violation	2	1%
Lost to follow-up	17	9%
Other	19	10%
incomplete termination data	1	1%

[a]Excludes major protocol violators

By-center analysis of disposition was notable for the fact that, at Site 777, seven of the 14 subjects randomized to sublingual treatment were discontinued due to "sponsor decision." Reckitt Benckiser explained that enrollment at this site began later than at the other two sites, and that subjects who had not completed study dosing by July 3, 2008 were terminated at "sponsor's decision" in order to allow the study database to be closed on schedule.

9.2.2.1.2.2 Demographics

The table below illustrates demographic and baseline characteristics of the sublingual administration treatment group. Overall, 99% of the subjects were white (there was one Asian subject and one African American; all others were white. No subjects were of Hispanic/Latino ethnicity), 64% of the subjects were male, and the average age was approximately 36 years (range 19-71 years), with over half of the participants in the 21-35 age group. At baseline, 99% had no oral mucosal abnormality.

Demographics in Study RB-US-07-0001

Age (years)		
Mean		36.1
Std		10.19
Median		34
Minimum		19
Maximum		71
Age Category (years)		
	< 21	4 (2.1%)
	21 - 35	102 (52.6%)
	36 - 50	71 (36.6%)
	> 50	17 (8.8%)
Sex - N (%)		
Male		124 (63.9%)
Female		70 (36.1%)
Race - N (%)		
American Indian		0
Asian		1 (0.5%)
Black or African American		1 (0.5%)
Native Hawaiian or Pacific Islander		0
White		192 (99.0%)
Other		0
Not reported		0
Severity of Oral Mucosa		
	Grade 0	192 (99.0%)
	Grade 1	2 (1%)
	Grade 2	0
	Grade 3	0

9.2.2.1.3 Dosing Information

The protocol specified that a ten-day supply of study drug (one-week supply plus enough for an extra three days) was to be dispensed during Week 1 (Visit 2); a two-week supply (plus three days' extra) was to be dispensed during Weeks 2, 4, 6, 8, and 10 (Visits 3 to 7). However, at the site enrolling the majority of the patients, the procedures for Visit 2 were combined with Visit 1 and it is unclear when the first study drug supply was dispensed. The case report form was designed in such a way that the Visit 2 drug dispensing was recorded as "number of strips" while subsequent visits were recorded separately as a number of strips for each of the various available dosage strengths.

As subjects had already been on a stabilized dose of buprenorphine and naloxone for at least 30 days, it was expected that the same dose of study drug would be well tolerated. However, adjustments were allowed at the discretion of the Investigator. Dose adjustments were recorded in the CRF. No doses higher than 32 mg per day were permitted per protocol.

Enrolled subjects were taking a wide range of dose regimens at baseline. In contradiction to the label, which calls for a single daily dose, the vast majority of enrolled subjects were taking their pre-study medication in multiple daily doses. This is difficult to explain pharmacologically because buprenorphine has a very long duration of action, which exceeds its persistence in plasma, and several researchers and clinicians have advocated less-than-daily dosing as a viable maintenance strategy. Reckitt Benckiser was asked for an explanation of the unusual dosing regimens reported by study subjects and explained that

> RBP has recent information from a consumer practices and attitudes survey conducted between August and September 2008 in 321 current Suboxone users covering 41 states. The average length of therapy with Suboxone was 12 months, ranging from 1-72 months. The data indicated that patients may sometimes take ¼ or ½ of a 2/0.5 mg or 8/2 mg Suboxone tablet, and that for patients who take two, three, or four doses throughout the day, the doses are not necessarily the same. Most commonly, respondents took Suboxone twice daily (46%), followed by once daily (29%), three times daily (15%), and four or more times daily (10%). Thus, the data from this survey are consistent with the Division's observation above that only one-third of the patients in study 0001 were taking a single daily dose of Suboxone. The most common first dose reported in the survey included either ½, 1, or 2 of an 8/2 mg tablet. Additionally, 58% of these respondents split tablets to achieve their target daily dose; respondents who split tablets were, on average, taking less Suboxone and less of the 2/0.5 mg tablets compared to those who did not split.

Thus, the enrolled subjects may have been representative of "real world" use of Suboxone which is pharmacologically illogical and counter to the labeling.

Further complicating the characterization of baseline Suboxone use, the Case Report Form offered a field for "dose" and one for "frequency." While Reckitt reports that "In the study's CRF completion guidelines for prior medications (including pre-study Suboxone), it is indicated (in bold text) that the "dose" variable should be reported as ***total daily dose***," it appears that at least some CRFs were completed such that the "dose" represented the dose taken on each occasion where multiple daily doses were used. This can be inferred from comparing the pre-study Suboxone dose to the dose dispensed at Visit 3, where a number of subjects listed with "dose" 8 mg and "frequency" b.i.d. were dispensed a total daily dose of 16 mg.

It is impossible to determine precisely what dosing regimens were being used by patients during the study. The case report form captured a "total" dose for study drug, and had fields for number of strips dispensed at each dosage strength, but did not capture a dosing regimen. The regimen can be inferred from the relationship between the total dose and the supplies of study drug dispensed. For example, many subjects with a total dose of 16 mg were given their supplies in 8 mg strips, rather than a single 16 mg strip per day, or were even dispensed very large supplies of 2 mg strips.

In summary, unusual features of the case report form design and data capture make it difficult to interpret the information on dosing. However, it appears that most enrolled participants were treated with doses between 4 and 32 mg/day in multiple divided doses.

Based on analysis of the drug dispensing dataset, it appears that there were 126 subjects assigned to sublingual treatment who attended six drug dispensing visits.

9.2.2.1.4 Protocol Violations

Protocol violations included enrollment of patients who were not taking the protocol-specified minimum dose of medication and patients who had not been on medication for the protocol-specified minimum duration of 30 days, or patients who exceeded the maximum age. Very few patients were discontinued for reasons classified as "protocol violation." However, protocol "deviations" were extremely common. Out-of-window visits, missing drug screens or pregnancy tests, and questionnaires which were not administered occurred with some frequency. (The data submitted were not amenable to tabulation and no effort was made by the applicant to group similar "deviations" such as "Visit 9 Questionnaire Not Done" and "Visit 9 Questionnaire Was Not Done" for the purpose of analysis.)

At site 333, which enrolled the vast majority of participants, the failure to return study drug or empty packets as required was recorded as a deviation. Accordingly, at this site, 74% of subjects had a protocol deviation. At the other two sites, failure to return study medication was not recorded as a deviation, although Reckitt Benckiser later provided a list of such deviations and they were nearly universal at the other sites as well.

Overall, these violations/deviations and the inconsistency of recording and reporting them simply reflects the general poor conduct of the study.

9.2.2.2 Efficacy Results

Not applicable

9.2.2.3 Safety Results

9.2.2.4.1 Deaths

There were no deaths in the development program for Suboxone film strips.

9.2.2.4.2 Nonfatal Serious Adverse Events

Six SAEs were reported. Of these, several were clearly unrelated to study drug (all were assessed as unrelated by the sponsor). The table below briefly lists the events, brief narratives, and my assessment of relatedness. Events from both the sublingual group and the buccal group are included in this presentation for completeness.

One of the events is suggestive of precipitated withdrawal, and may therefore be related to the enhanced bioavailability of the naloxone component in the new formulation.

Patient	Event Description	Narrative	Reviewer Comment
Sublingual			
333010 35 yo F	Injuries sustained as a passenger in an MVA	SAE: injury to right upper extremity (MedDRA preferred term: skin injury) This 35-year-old woman who received her first dose of study drug (16 mg buprenorphine and naloxone soluble film) sublingually on 27 February 2008 was hospitalized from (b) (6) for injuries sustained during a motor vehicle accident in which she a was a passenger.	Unrelated
333073 32 yo F	Cervical cancer dx after ~2 months on study drug	SAE: squamous cell carcinoma of the cervix This 32-year-old female who received her first dose of study sublingually on 8 February 2008 was diagnosed on (b) (6) with squamous cell carcinoma of the cervix	Unrelated
333233 31 yo M	Kidney stones in pt w/previous h/o kidney stones, dx after ~5 wks on study drug	SAE: kidney stones (MedDRA preferred term: nephrolithiasis) This 31-year-old male with a medical history significant for chronic kidney stones received his first dose of study drug (8 mg buprenorphine and naloxone soluble film) sublingually on 21 March 2008 and was diagnosed with kidney stones requiring hospitalization on (b) (6). The subject completed the study, receiving his last dose of study drug on 2 July 2008.	Unrelated
333149 49 yo M	Nausea, chest pain, vasovagal syncope w/injury during initiation of study drug treatment at high dose	SAE: vasovagal event (MedDRA preferred term: syncope vasovagal) This 49-year-old male received his first dose of study drug (32 mg buprenorphine and naloxone soluble film) sublingually on 3 March 2008. On 4 March 2008, the subject reported vomiting, which was classified as severe in intensity. On (b) (6), the subject experienced nausea, chest pain, and vasovagal syncope, during which he fell and lacerated his left ear. Although the sponsor classified this event as unrelated to study drug, all the reported symptoms could conceivably be related to withdrawal, as the subject was receiving a cumulative dose of 8 mg naloxone and may have experienced precipitated withdrawal. Ultimately, the subject completed the study, receiving a fnal dose of study drug on 27 May 2008	Possibly related
Buccal			
111011 37 yo M	MVA, no details, ~wk 5 of study drug	SAE: motor vehicle accident (MedDRA preferred term: road traffic accident) This 37-year-old male received his first dose of study drug (6 mg buprenorphine and naloxone soluble film) on 4 March 2008 via the buccal route. On (b) (6), the subject was involved in a motor vehicle and was hospitalized. The outcome was unknown and the subject was lost to follow-up.	Cannot assess
111047 30 yo M	Esophageal cancer dx ~wk 6 of study drug	SAE: esophageal cancer (MedDRA preferred term: oesophageal carcinoma) This 30-year-old male received his first dose of study drug (6 mg buprenorphine and naloxone soluble film) on 13 March 2008 via the buccal route. In early (b) (6), he was hospitalized and diagnosed with esophageal cancer. The subject withdrew his consent to participate in the study on 5 May 2008.	Unrelated

9.2.2.4.3 Dropouts and/or Discontinuations

Reckitt Benckiser's report lists five subjects as discontinuing due to adverse events in the sublingual treatment group and three in the buccal treatment group. However, three of these appear to have been discontinuations due to protocol violations (two subjects became pregnant; one subject took prohibited medication for a concurrent medical problem). One of the subjects is described in this section as discontinuing due to an SAE of road traffic accident but appears to have been lost to follow-up. Notably, two subjects appear to have discontinued due to treatment-emergent symptoms suggestive of precipitated withdrawal. In addition, one subject who became pregnant while using the study drug subsequently miscarried.

Sublingual Arm:

Subject 333010 This subject was discontinued because of an SAE (injuries sustained in motor vehicle accident) (see above).

Subject 333049 (Pregnancy; Abortion spontaneous): 31-year-old female began treatment with study drug (16 mg buprenorphine and naloxone soluble film) sublingually on February 27, 2008. On May 14, 2008, the subject reported that she was pregnant and was discontinued from the study that same day. (It is not reported whether she was continued on Suboxone tablets or discontinued buprenorphine altogether.) On June 1, 2008 she had a spontaneous abortion. The sponsor considered this unrelated to study drug. Reviewer assessment is that relatedness cannot be ruled out.

Subject 333129 (Vision blurred; Constipation; Poisoning; Disturbance in attention; Headache; Insomnia; Withdrawal syndrome; Hyperhidrosis): 39-year-old male was randomized to sublingual treatment on February 29, 2008 and was provided 20 film strips (dose not specified in CRF). The CRF indicates that the patient reported on March 7 that on the first day of dosing, he experienced "headache, intoxication, decreased mental clarity, loss of focus, worsening withdrawal syndrome, constipation, insomnia, and sweating." He discontinued study drug although it is not clear when; only 9 of the 20 film strips were returned. Note that the MedDRA code "vision blurred" appears to be erroneous; in context the term "loss of focus" does not appear to refer to visual acuity.

Subject (b) (6)**/333235 (Arthralgia)**: 39-year-old male received his first dose of study drug (24 mg buprenorphine and naloxone soluble film) sublingually on March 24, 2008. On June 11, 2008, the subject experienced worsening of left knee pain. The sponsor indicates in the submission that this subject was permanently discontinued on June 13, 2008 due to the event of arthralgia. However, the case report form indicates that the patient was discontinued due to a protocol violation, because he was taking Percocet and Oxycontin, evidently related to knee pain, which was not recorded as an AE at the time but added as a site-generated clarification later on.

Subject (b) (6)**/333253 (Pregnancy)**: 31-year-old female received her first dose of study drug (16 mg buprenorphine and naloxone soluble film) sublingually on March 28, 2008. On May 29, 2008, the subject reported that she had become pregnant. She was discontinued from the study on May 29, 2008 due to the pregnancy, which was considered a protocol violation.

Buccal Arm:
Subject (b) (6)/111011 (Road traffic accident): This subject was described has having discontinued because of an SAE; however the detail regarding the SAE suggests the subject was lost to follow-up.

Subject (b) (6)/111047 (Oesophageal carcinoma): This subject voluntarily withdrew consent because of an SAE (see above)

Subject (b) (6)/333222 (Nausea; Back pain; Migraine; Somnolence): 38-year-old male received his first dose of study drug (16 mg buprenorphine and naloxone soluble film) buccally on March 19, 2008. On March 21, 2008, the subject experienced symptoms which he described in the dose preference questionnaire as "gave me extreme [sic] headaches, sick, moore [sic] back pain." These complaints were coded as "nausea, back pain, migraine, and somnolence," (although the CRF originally said "withdrawal") all which were considered to be moderate in severity and probably related to study drug. Apparently the subject continued on drug until March 29th but then withdrew his consent to participate in the study on March 31, 2008 because of these events.

9.2.2.4.4 Submission Specific Primary Safety Concerns

9.2.2.4.4.1 Oral Mucosal Tolerability

Study RB-US-07-001 was conducted primarily to identify any new safety concerns related to the delivery of the buprenorphine/naloxone combination in a new dosage form, a soluble filmstrip for transmucosal delivery. No products using this type of delivery system are marketed, although the technology is similar to the strips used for oral delivery of cough/cold products and breath fresheners. Special attention was given to evidence of local oral irritation.

Oral exams were conducted at each visit, albeit not by dental professionals or others specifically qualified to evaluate the oral mucosa. It is likely only the most obvious and dramatic of oral mucosal abnormalities would have been detected in this way. The protocol stipulated that any abnormal findings were to be recorded both as an oral exam score but also as an adverse event, however, this appears to have been done inconsistently.

Overall, 10 of the 194 subjects randomized to treatment with sublingual study drug had either a treatment-emergent abnormal exam recorded, or a spontaneous adverse event referable to the mouth/tongue/oral mucosa. No patient had both.

9.2.2.4.4.1.1 Oral Exams

Reckitt Benckiser provided (at Agency request) a tabulation of the cumulative numbers of patients who completed various numbers of the protocol-specified examinations. According to their tabulations, they concluded that 121 subjects completed an oral mucosa exam at visit 10 and at all previous visits. However, as noted above, Visits 1 and 2 were combined in many cases, and therefore, this represented 9 mucosal exams for these subjects. Review of the submitted datasets located 9 or 10 exam results for 120 (not 121) subjects as shown below.

Of the 194 subjects randomized to treatment with sublingual study drug, exam results were recorded for all 10 protocol-specified exams for 44, and for 9 exams for an additional 86 subjects.

Number of Exams Recorded	Number (%) of Subjects	
1	6	3%
2	13	7%
3	8	4%
4	6	3%
5	6	3%
6	8	4%
7	9	5%
8	8	4%
9	86	44%
10	44	23%

Many of these exams were apparently recorded outside prototol-specified time windows and were therefore excluded by Reckitt Benckiser from their analyses. For this reason, I have not presented any of the sponsor's analyses because abnormalities arising at any time are of interest, even if they are recorded outside a specified window.

The overwhelming majority of the oral exams were graded as "0" (normal mucosa).
Only 6 study participants treated with sublingual study drug had an abnormal exam at any time during the study. One additional patient (333073) has an adverse event of "oral mucosal exam=grade 1 abnormality" recorded in the AE dataset but no abnormal exam recorded in the Oral Exam dataset.

Three patients had Grade 1 abnormalities at screening. Of these, one patient had Grade 0 exams recorded at Visits 2-10 and one patient had a second exam with Grade 1 abnormality at Visit 2 but no further exams recorded until Visits 9 and 10, at which time Grade 0 exams were recorded. The last patient had Grade 1 abnormality at screening and no further exams were recorded. Two patients had transient abnormalities (Grade 2 abnormality at Visit 4; Grade 1 abnormality at Visit 3) with Grade 0 exams recorded at all other visits. Finally, a single patient with Grade 0 exams at baseline through Visit 9 had a Grade 2 abnormality recorded at Visit 10.

In summary, these exams provided little evidence of treatment-emergent mucosal abnormalities, but may have lacked sensitivity due to the lack of training of the examiners. Furthermore, as will be discussed below, the dosing regimen employed by the vast majority of subjects differs substantially from the recommended dosing regimen in the label. Specifically, almost no patients were using a single daily dose of study drug; therefore the data represent findings collected in the setting of patients using small, divided doses rather than the specific doses in labeling. Indeed, because a 16 mg strip was provided for the study but is not proposed for marketing, it is unlikely that any patient would have been treated with two 8 mg strips simultaneously, as recommended

in the labeling as the target dose for all patients. Therefore, although no concerning findings were generated in this study, it may provide little reassurance about the product when used according to the proposed labeling.

9.2.2.4.4.1.2 Adverse Events Related to the Mouth

A string search in the verbatim term field and the MedDRA LLT field for "mouth," "oral," "gum," "ging," "gloss," "oral," and "tongue" was used to supplement the HLGT "Oral Soft Tissue Conditions." Using this method, nine patients reporting events referable to the mouth, tongue, and oral mucosa were identified. These included three patients for whom the AE was an oral exam abnormality and six for whom the AE was a spontaneously-reported AE. Notably, there were no spontaneous complaints from the three subjects with oral mucosal abnormalities on exam. In addition, there were two patients for whom oral mucosal exam abnormalities were recorded in the Oral Exam database who were not listed in the AE dataset. Notably, these two patients also had no spontaneously-reported oral complaints.

Complaints reported spontaneously included:

Preferred Term	# of Patients
GLOSSODYNIA (includes verbatim terms burning of tongue, burning tip of tongue, tongue tender)	3
HYPOAESTHESIA ORAL (includes verbatim term numbness tongue)	2
TONGUE COATED	1

9.2.2.4.4.2 Study Drug Accountability/Diversion

The protocol called for dispensing approximately three extra days' supply of study drug at each visit to account for variations in scheduling. Unused drug was to be collected at each visit and a "percent compliance" calculated based on the amount returned. In the dataset for drug accountability, this variable is blank for 1707/2497 (68%) rows, because there is no record of the study drug returned, suggesting that there was poor attention to this aspect of the protocol. In the 32% of visits for which there is a "percent compliance" recorded, it is over 100% in 28% of cases, indicating that subjects failed to return excess study drug supply. Taken together with multiple reports of lost or stolen study drug, or missing empty packets, this suggests that there may have been significant diversion of study drug supply. Although there is no definite evidence that this is the case, (b) (4)

A search of the protocol deviation dataset using terms such as *lost, stolen, packet, strips, failed, return, missing* yielded several hundred listings which were inspected to remove events unrelated to study drug accountability. This yielded 294 events reported in 155 different patients (all at site

333, where total enrollment was 233) in which empty packets were not returned, unused study drug was not returned as required, or study drug was reported lost, stolen, or destroyed. About half of the patients had one such report but two or three reports by the same patient were common, and 6 patients had as many as 6-7 such violations. No action appears to have been taken by the study site.

Only Site 333 reported these events as protocol deviations. At Agency request, Reckitt Benckiser provided (in line listing form only, not a dataset amenable to analysis) a listing of patients with similar deviations at the other two sites. This revealed 18 (of 27 enrolled) patients at Site 777 with "missing" study drug supply (none "lost" or "stolen") and 118 (of 122 enrolled) patients at Site 111 with missing, stolen, or lost drug supply. Most of these patients are listed as having "missing" packets on only a single occasion; however, some are missing substantial quantities of packets (up to 377 packets at one visit), and some patients reported "stolen" or "lost" unused drug supplies on more than a single occasion.

At Agency request, Reckitt Benckiser provided a tabulation showing how many strips of each dosage strength were "prescribed" to patients (i.e., the amount the patient was instructed to use), how many were "dispensed" (patients were to get either a one- or two-week supply of medication, plus an additional three-day supply) and how many strips were returned, calculating the number of strips which were unaccounted for. In this tabulation, if a patient were dispensed medication and he/she did not return to the clinic prior to Visit 9 (or at all), the amount prescribed was considered to be zero, which elevates the calculation of the amount of drug considered to be "missing." Overall, 12,900 strips were provided to participants in excess of the amount prescribed. Of these, 5918 (46%) were not returned. Across sites the amount of missing study drug ranged from 38% of the strips due to be returned at Site 333 to 90% of the strips due to be returned at Site 777.

No information on accountability of drug supply for the tablet formulation is available, because the registration studies were done under supervised administration conditions (and in some cases used a liquid formulation). (b) (4)

9.2.2.4.5 Common Adverse Events

Adverse events were collected by spontaneous report at study visits and coded using MedDRA. However, to facilitate comparison to the existing safety experience with the approved sublingual tablets, the MedDRA terms were mapped to corresponding COSTART terms. The tables below illustrate the COSTART-coded common adverse events in Study RB-US-07-0001. Compared to the pivotal studies included in the approved labeling for Suboxone and Subutex, there was a substantially lower rate of adverse events reported. This may relate to the difference in population (stabilized at least 30 days vs. new entrants to treatment) or may reflect the overall cavalier conduct of Study RB-US-07-0001.

Adverse Events reported in at least 2% of participants, by COSTART Body System and Preferred Term in Study RB-US-07-0001

Body System/Adverse Event (COSTART Terminology)	Sublingual N=194 n (%)	Buccal N=188 n (%)	Total N=382 n (%)
At least one adverse event	54 (27.8%)	62 (33.0%)	116 (30.4%)
Body as a Whole	29 (14.9%)	34 (18.1%)	63 (16.5%)
Pain	8 (4.1%)	7 (3.7%)	15 (3.9%)
Accidental injury	5 (2.6%)	9 (4.8%)	14 (3.7%)
Infection	6 (3.1%)	7 (3.7%)	13 (3.4%)
Headache	2 (1.0%)	4 (2.1%)	6 (1.6%)
Skin and Appendages	7 (3.6%)	6 (3.2%)	13 (3.4%)
Rash	2 (1.0%)	6 (3.2%)	8 (2.1%)
Respiratory System	6 (3.1%)	5 (2.7%)	11 (2.9%)
Sinusitis	3 (1.5%)	4 (2.1%)	7 (1.8%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.
Data derived from: Clinical Study Report for RB-US-07-0001, Statistical Table 13.1.2.

9.2.2.4.6 Laboratory Findings, Vital Signs, Electrocardiograms

Clinical laboratory (hematology, clinical chemistry, and clinical urinalysis), physical examination, ECG, and vital sign data were not collected.

9.3 Studies Referenced Demonstrating Evidence Of Efficacy For Suboxone Tablets

The efficacy of buprenorphine and the buprenorphine/naloxone combination tablet in the treatment of opiate addiction was supported primarily by two studies involving buprenorphine sublingual solution and one study of the sublingual tablets (both buprenorphine-only and combination). These included a study comparing buprenorphine sublingual solution, 8 mg/day, to methadone (CR88/130), a dose-controlled study of buprenorphine sublingual solution (CR92/099) with a flexible-dose open-label follow-on (CR92/100), and a four-week study comparing Subutex 16 mg/day, Suboxone 16 mg/day, and placebo, with an open-label, flexible-dose follow-on (CR96/013 and CR96/014, also known as 1008a&b[7]).

The design and results of these studies are described below. Most of this is taken from, or modified from, my Team Leader review of NDA 20-733.

9.3.1 Study CR88/130

The first study, given Reckitt & Colman reference number CR88/130, was a double-blind, double-dummy, parallel-group, trial comparing buprenorphine sublingual solution 8 mg/day with oral methadone 20 and 60 mg/day, and consisting of a one-week induction phase, 16-week maintenance phase and a 7-week detoxification phase. In this study, 162 subjects were randomized to receive sublingual buprenorphine 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of Subutex or Suboxone), or two relatively low doses of methadone, 20 mg/day and 60 mg/day. Buprenorphine was titrated to maintenance dose by day three; methadone doses were titrated more gradually according to the table below.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-9	Day 10-Week 17
Buprenorphine	2 mg	4 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Methadone 20	20 mg	30	30	30	30	25	20 mg
Methadone 60	20 mg	30 mg	40 mg	50 mg	60 mg	60 mg	60 mg

Maintenance dosing continued through week 17. Subjects received individual and/or group counseling weekly. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opiates, the reviewers concluded that the study provided evidence that buprenorphine was more effective than methadone, 20 mg p.o. q.d, in keeping heroin addicts in treatment and in reducing their use of opiates while in treatment. The

[7] This study was conducted under a single protocol calling for a placebo-controlled 4-week study, followed by open-label, flexible dose treatment open to completers of the placebo-controlled study as well as new entrants. Several reference numbers have been assigned to the study. For consistency, the reference numbers for the sponsor's study report (CR number), and not the protocol numbers, have been used in this memo. Study 1008 included substudies 1008a and 1008b. The subjects who participated in placebo-controlled portion were considered to have enrolled in 1008a. New entrants directly into open-label treatment were considered to have enrolled in 1008b. The study report given reference number CR96/013 comprises the open-label phase of Study 1008a. Study CR96/014 included participants in 1008a who continued into the open-label, flexible dose extension (1008a, Phase II), and new subjects enrolled directly into open-label, flexible dose treatment (1008b). Other terms used by the sponsor are "the efficacy study" (CR96/013 a.k.a 1008a, Phase I) and "the safety study" (CR96/014, a.k.a. 1008a, Phase II + 1008b).

effectiveness of buprenorphine was in the same range as methadone, 60 mg p.o. q.d., but neither superiority nor equivalence was demonstrated.

At the conclusion of the maintenance period, medications were tapered by approximately 20-30% per week over weeks 18-24, with placebo dosing for the last two weeks.

9.3.2 Study CR92/099

The second study, CR92/099, was a twelve-center, double-blind, parallel-group, 16-week trial of four doses of buprenorphine sublingual solution. The primary aim of this study was to determine the safety and effectiveness of 8 mg/day buprenorphine sublingual solution as compared to 1 mg/day in decreasing illicit opiate use. The 1 mg dose was envisioned as an ethical alternative to placebo. A secondary purpose was to gather experience with 4 mg and 16 mg daily dosing. In this study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution . Buprenorphine was titrated to maintenance doses over 1-4 days (see table below) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site. Subjects completing the study could enroll in an open-label, flexible-dose extension study which included at least one hour per month of counseling or psychosocial services.

Buprenorphine dose	Day 1	Day 2	Day 3	Maintenance dose
1 mg	1 mg	1 mg	1 mg	1 mg
4 mg	2 mg	4 mg	4 mg	4 mg
8 mg	2 mg	4 mg	8 mg	8 mg
16 mg	2 mg	4 mg	8mg	16 mg

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opiates, the reviewers concluded that this study provided evidence that sublingual buprenorphine solution, 8 mg/day, is more effective than 1 mg/day in keeping heroin addicts in treatment and in reducing their use of heroin. There was an indication that 16 mg/day is somewhat more effective than 8 mg/day, and that 4 mg/day is more effective than 1 mg/day. There was no indication that 4 mg/day was different from 8 mg/day.

9.3.3 Studies of Buprenorphine Sublingual Tablets

One study in support of the to-be-marketed tablet formulations (both the buprenorphine-only and the buprenorphine + naloxone tablet) was submitted to NDA 20-732. The study was a multicenter, clinical trial conducted in two phases. The first, 4-week phase (Study CR96/013 or 1008A) was conducted at eight sites as a randomized, placebo controlled, double blind efficacy assessment. Subjects were to be randomly assigned to one of three treatment groups: placebo, buprenorphine 16 mg per day, or buprenorphine 16 mg/naloxone 4 mg per day. The second phase of the study (phase 2 of Study 1008A and Study 1008B conducted at four additional sites, known together as CR96/014) was a 48- to 52-week open label safety assessment of the buprenorphine/naloxone arm only, in doses up to 24 mg/6 mg per day.

In the double-blind phase of the study, 326 subjects were randomly assigned to one of three treatment groups: placebo, buprenorphine 16 mg per day, or buprenorphine 16 mg/naloxone 4 mg per day. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Drug was to be taken once daily sublingually. The subject was to be instructed to hold the medication under his/her tongue for approximately 5 to 10 minutes until completely dissolved in order to ensure maximum absorption. Induction (for those in the active drug treatment groups) was accomplished using buprenorphine 8 mg SL tablet on day one, and buprenorphine SL tablet 2 x 8 mg beginning on day two. (Subjects in the buprenorphine/naloxone condition began treatment with the combination tablet on day three.) Subjects received a session of HIV education and one hour of individual counseling per week. The data showed that subjects treated with buprenorphine, whether administered as monotherapy or in combination with naloxone, had a statistically significantly higher percentage of urine samples that were negative for opiates when compared to the subjects who were treated with placebo: 19.7% clean urines following monotherapy, and 16.7% following combination therapy, and 5.7% for placebo. There was no statistically significant difference between the two buprenorphine treatment arms, nor was equivalence demonstrated.

9.3.4 Efficacy conclusions

Taken alone, the single study of Suboxone and Subutex vs. placebo (CR96/013) would not have provided the substantial evidence needed for approval of either product. Information from trials using other formulations was used to support the claim of efficacy. Information about the pharmacokinetics of the to-be-marketed formulation indicated that the 16 mg dose of the Suboxone tablet (2 x 8 mg tablets) is bioequivalent to a dose of approximately 12 mg of solution. Two trials using buprenorphine sublingual solution demonstrated the efficacy of the 8 mg/day dose of solution. One of those trials also provided evidence of efficacy of the 16 mg/day dose of solution. Therefore, since there was substantial evidence of efficacy for a dose lower than the 2 x 8 mg tablet regimen (i.e. 8 mg sublingual solution), and some evidence of efficacy for a dose higher than the 2 x 8 mg tablet regimen (i.e. 16 mg sublingual solution), in reviewing the applications, I concluded that these studies of the sublingual solution should be viewed as confirmation of the findings of Study CR96/013. Furthermore, since the studies of the sublingual solution showed that doses across a range which brackets the 2 x 8 mg regimen demonstrated efficacy in longer studies (16 weeks), the short duration of the CR96/013 study, which would otherwise render it somewhat unpersuasive, was offset by the available data from the other studies.

9.4 Worldwide Marketing Status of Buprenorphine Products

Note: Schering Plough, not Reckitt Benckiser, markets buprenorphine products throughout most of the world. Reckitt Benckiser confirmed through Schering Plough regulatory that in the tables below,

> "discontinued" means that Schering Plough stopped supplying the product to the market, and allowed the registration become inactive. "Withdrawn" means that Schering Plough pulled the registration from the market. "Not on sale" means Schering Plough never launched the product/strength in that particular market.

Schering Plough indicated any discontinuation or withdrawal was due solely to commercial interests, and not due to any adverse events or other medical/safety issues.

Subutex and Suboxone - Approvals and Sales Status

Country	Subutex		Suboxone	
	Approval date	Launch date	Approval date	Launch date
EUROPEAN UNION				
Austria	28/06/99	01/08/99 0.4mg-not marketed	26/09/06	10/09/07
Belgium	14/02/00	01/10/01 0.4mg-not marketed	26/09/06	09/06/08
Bulgaria	29/12/06	Pending	26/09/06	30/11/07
Cyprus	17/04/06	Pending	26/09/06	Pending
Czech Republic	01/03/00 14/12/05	01/07/00-Withdrawn 01/07/00	26/09/06	12/01/08
Denmark	14/05/99	20/09/99	26/09/06	01/01/07
Estonia	26/08/05 (Repeat Use)	26/08/05 0.4mg-not marketed	26/09/06	10/12/07
Finland	15/02/99	19/10/99	26/09/06	20/03/07
France	31/07/95	16/02/96	26/09/06	Pending
Germany	06/01/00	01/02/00	26/09/06	01/03/07
Greece	07/06/00	01/07/01 0.4mg-not marketed	26/09/06	Pending
Hungary	05/10/05 (Repeat Use)	12/02/08 0.4mg and 8mg-not marketed	26/09/06	23/11/07
Ireland	16/08/02	09/06/06	26/09/06	23/02/07
Italy	02/12/99	15/02/00 0.4mg-not marketed	26/09/06	Pending
Latvia	11/07/03	19/10/05 0.4mg-not marketed	26/09/06	Pending

Country	Subutex		Suboxone	
	Approval date	Launch date	Approval date	Launch date
Lithuania	16/11/05 (Repeat Use)	16/11/05 0.4mg-not marketed	26/09/06	23/01/08
Luxembourg	08/07/98	01/03/99 0.4mg-not marketed	26/09/06	09/06/08
Malta	18/01/06		26/09/06	01/01/08
Netherlands	06/02/06	01/11/07	26/09/06	16/04/07
Poland	28/10/05	Pending	26/09/06	Pending
Portugal	23/12/99	01/06/00	26/09/06	01/09/07
Romania			26/09/06	19/11/07
Slovak Republic	12/05/00 29/01/06 (Repeat Use)	01/01/01-discontinued	26/09/06	12/09/07
Slovenia	16/02/04		26/09/06	02/07/07
Spain	12/04/00	0.4mg-withdrawn 2mg and 8mg-not currently marketed	26/09/06	Pending
Sweden	07/10/99	01/01/00	26/09/06	15/02/07
UK	22/12/98	18/01/99	26/09/06	01/12/06
OTHER EUROPEAN COUNTRIES				
Croatia	06/06/02		10/04/08	Pending
Iceland	03/08/99	01/11/99	24/10/06	28/05/07
Lichtenstein	22/12//98	03/01/00 0.4mg-Discontinued	02/09	
Norway	17/01/00	01/04/00	26/10/06	01/02/07
Switzerland	22/12/98	03/01/00 0.4mg-Discontinued	02/09	
REST OF WORLD				
Argentina	09/12/97	Not marketed		
Australia	02/11/00	16/03/01	27/07/05	01/04/06
Bosnia/Herzegovina			31/12/07	Pending
Canada	21/01/05	Not marketed	18/05/07	26/11/07
Colombia	24/07/01	Not marketed		
Hong Kong	07/04/00	01/02/01 0.4mg-withdrawn	31/12/07	Pre-approval use
Indonesia	26/03/02	01/04/02 0.4mg-not marketed	18/12/07	

Country	Subutex		Suboxone	
	Approval date	**Launch date**	**Approval date**	**Launch date**
Israel	28/01/01	12/05/01 0.4mg-discontinued		
Malaysia	07/06/01	01/11/01	24/08/06	25/11/06
Mexico	03/07/03	Not marketed		
New Zealand			17/01/05	11/05
Singapore	03/02/00	01/11/01	20/02/08	
South Africa	15/11/02	23/05/03 0.4mg-not marketed	03/09	
Syrian Arab Republic	09/10/00	Not marketed		
Taiwan	02/09		02/09	
Thailand	Pending		Pending	
Turkey			Pending	
UAE	01/06/01	Not marketed		
USA	08/11/02	01/04/03	08/10/02	01/04/03
	46 approved	**31 launched**	**43 approved**	**27 launched**

Temgesic (Buprenex / Buprex / Lepetan) - Approvals and Sales Status

Country	Sterile Injection		Sublingual tablet			Sublingual tablet	
	0.3 mg buprenorphine		0.2 mg buprenorphine	0.4 mg buprenorphine		0.2 mg buprenorphine + 0.18 mg naloxone	
	Approval	Status	Approval	Approval	Status	Approval	Status
EUROPEAN UNION							
Austria	31/03/88	Not marketed	30/03/84	11/07/97	On sale		
Belgium	13/03/79	On sale	30/04/83		On sale		
Czech Republic	31/07/84	Withdrawn	31/10/84		Withdrawn		
Denmark	28/02/80	On sale	31/3/82	31/03/90	On sale		
Finland	31/05/81	On sale	30/09/82	31/01/92	On sale		
France	17/07/84	On sale	17/04/87		On sale		
Germany	22/08/80	On sale	22/12/82	07/06/94	On sale		
Greece	30/09/81	Discontinued	28/01/82		Discontinued		
Hungary	31/07/87		28/02/90				
Ireland	28/02/78	On sale	30/06/80		On sale		
Italy	05/04/84	On sale	05/04/84	05/04/84	On sale 0.4mg-Withdrawn		
Luxembourg	09/04/96	On sale	09/04/96		On sale		
Netherlands	28/06/81	On sale	24/04/89	01/11/93	On sale		
Poland			12/02/91		Not marketed		
Portugal	19/08/83	On sale	19/08/83		On sale		
Slovak Republic	05/05/98	On sale	05/05/98		On sale		
Spain	06/09/84	On sale	06/11/85		On sale		
Sweden	30/11/81	On sale	07/11/86	30/09/90	On sale		
UK	03/10/77	On sale	11/11/80	25/10/90	On sale		

Country	Sterile Injection		Sublingual tablet			Sublingual tablet	
	0.3 mg buprenorphine		0.2 mg buprenorphine	0.4 mg buprenorphine		0.2 mg buprenorphine + 0.18 mg naloxone	
	Approval	Status	Approval	Approval	Status	Approval	Status
OTHER EUROPEAN							
Iceland	31/09/83	On sale					
Lichtenstein	01/01/98	On sale	01/01/98		On sale		
Norway	30/04/80	On sale	03/03/83	28/02/91	On sale		
Switzerland	31/10/79	On sale	31/03/83	30/09/91	On sale		
REST OF WORLD							
Algeria	26/08/97	On sale	01/09/98		On sale		
Argentina	20/05/83	Not marketed	11/09/91		Not marketed		
Australia	03/08/82	On sale	02/07/92		On sale		
Bahrain			31/03/91				
Benin	23/03/95	On sale	23/03/95		On sale		
Botswana	08/09/04	On sale	08/09/04		On sale		
Brazil	09/03/88		09/03/88		0.2mg-Not marketed		
Burkina Faso			22/01/86		On sale		
Canada	27/09/94						
Cameroon	16/10/89	On sale	21/12/93		On sale		
Chad	30/11/93	On sale	07/12/93		On sale		
Chile	16/01/90	Discontinued	16/01/90		Discontinued		
Colombia	30/06/82	Discontinued	20/03/84		On sale		
Cote D'Ivoire	06/09/89	On sale	16/06/93		On sale		
Costa Rica	26/01/82	Discontinued	30/09/91		Discontinued		
Dominican Republic	21/05/82	Discontinued	06/04/93		Discontinued		
Ecuador	26/02/86	Discontinued	16/05/96		Discontinued		

Country	Sterile Injection		Sublingual tablet			Sublingual tablet	
	0.3 mg buprenorphine		0.2 mg buprenorphine	0.4 mg buprenorphine		0.2 mg buprenorphine + 0.18 mg naloxone	
	Approval	Status	Approval	Approval	Status	Approval	Status
El Salvador	01/04/81	Discontinued	25/09/91		Discontinued		
Gabon	05/03/90	On sale	04/11/92		On sale		
Guatemala	10/11/80	Discontinued	16/05/91		Discontinued		
Guinea	13/05/99	On sale	13/05/99		On sale		
Honduras	05/12/80	Discontinued	01/02/91		Discontinued		
Hong Kong	31/05/87	On sale	31/05/87		On sale		
Japan*	31/05/83	On sale					
Madagasgar	23/12/97	On sale	23/12/97		On sale		
Malaysia	23/02/87	Discontinued	23/02/87		Discontinued		
Mali	16/09/98	On sale	16/09/98		On sale		
Mauritius	22/12/97	On sale	22/12/97		On sale		
Mexico	30/10/89	On sale	31/10/91	01/04/94	On sale 0.4mg-not marketed		
Morocco	04/05/90	Not marketed	26/10/98		Not marketed		
New Zealand	24/05/79	On sale				14/6/90	Dis-continued 15/2/01
Nicaragua	11/02/81	Discontinued	07/11/94		Discontinued		
Oman			31/12/85				
Pakistan	22/05/79	Not marketed	07/10/81		Not marketed		
Panama	28/02/80	Discontinued	31/03/83		Discontinued		
Paraguay	11/02/91	Discontinued					
Peru	31/08/80	Discontinued	04/11/96		Discontinued		
Phillipines	22/07/85	Discontinued					
Singapore	11/01/98	Discontinued	11/01/98		Discontinued		

Country	Sterile Injection		Sublingual tablet			Sublingual tablet	
	0.3 mg buprenorphine		0.2 mg buprenorphine	0.4 mg buprenorphine		0.2 mg buprenorphine + 0.18 mg naloxone	
	Approval	Status	Approval	Approval	Status	Approval	Status
South Africa	30/03/98	On sale	30/03/98		On sale		
Sri Lanka	30/09/81		31/10/84				
Taiwan		On sale	08/04/97		On sale		
Thailand	21/04/99	Not marketed	21/04/99		Not marketed		
Turkey	30/10/99	Not marketed	30/10/99		Not marketed		
UAE	10/12/91		10/12/91				
Uruguay	15/04/85	Withdrawn					
USA	30/06/85	On sale					
Venezuela	27/09/88	Discontinued	20/09/90		Discontinued		
Zaire	31/03/86		31/03/86				
	67 approved	**37 on sale**	**64 approved**	**10 approved**	**36 on sale**	**1 approved**	**0 on sale**

* In Japan a Temgesic 0.2mg injection product is also registered.

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

/s/

Celia Winchell
7/15/2009 12:19:03 PM
MEDICAL OFFICER

Medical Officer Review

Date	6/17/09
From	Elizabeth Kilgore, MD
Subject	Review of Selected Safety Issues
NDA#	**NDA 22-410**
Applicant	Reckitt Benckiser
Date of Submission	
PDUFA Goal Date	August 21, 2009
Proprietary Name / Established (USAN) names	Suboxone (b) (4)
Dosage forms / Strength	Buprenorphine 8 mg with Naloxone 2mg and Buprenorphine 2 mg with Naloxone 0.5 mg
Proposed Indication(s)	1. Maintenance Treatment of Opioid Dependence 2. 3.
Recommended:	*(Approval vs. Approvable vs. Not Approvable vs. Complete Response)*

1 Background:

Buprenorphine is a μ-opioid receptor partial agonist and a κ-opioid receptor antagonist. Buprenorphine HCl is a narcotic analgesic which has been marketed since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain.

In 2002, two sublingual tablet formulations were approved for the treatment of opioid dependence: Subutex (buprenorphine only, NDA 20-732) and Suboxone (buprenorphine with naloxone intended to deter abuse, NDA 20-733). Naloxone is an opioid receptor antagonist that is poorly absorbed orally and is included in the preparation to deter intravenous use.

NDA 22-410 is being submitted for proposed Suboxone (b) (4) C-III (buprenorphine and naloxone soluble film) for sublingual administration. Suboxone (b) (4) is intended for the maintenance treatment of opioid dependence .The dosage strengths of Suboxone® (b) (4) for which marketing approval is being sought are the same as those currently approved for Suboxone sublingual tablets (buprenorphine 8mg with naloxone 2mg and buprenorphine 2mg with naloxone 0.5mg).

This review addresses three specific safety issues included in the NDA: hepatic safety, use in pregnancy, and accidental pediatric exposure.

2 Hepatic Safety

2.1 Background

In 2000, Petry[1] published a study entitled, "Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine" in which it was reported that among patients with a history of hepatitis, AST and ALT levels significantly increased with buprenorphine treatment.

The Petry finding was considered at the time of approval of Suboxone and Subutex but due to confounders, no conclusions could be drawn. The Applicant (Reckitt Benckiser) was asked to perform a post-marketing safety study addressing this issue.

The applicant reported that cases of cytolytic hepatitis and hepatitis with jaundice had been observed in the opioid-dependent population receiving buprenorphine in both their clinical trials and postmarketing adverse event reports (Reckitt Benckiser Report RC 020117, 2002).

[1] Petry NM et al. The American Journal of Addictions 9:265-269, 2000

The findings from the Agency and Reckitt Benckiser were reflected in the current label for NDA 20-732 and 20-733 (last revised 2006). Minor editorial changes to this labeling as proposed by Reckitt Benckiser, in the context of this NDA, are illustrated below using markup format:

(b) (4)

The *in vitro* and nonclinical work by Berson[2] suggested that high concentrations of buprenorphine are toxic to hepatic mitochondria. Buprenorphine may be toxic when used in large overdoses. Berson and colleagues referred to a case reported by Houdret of severe acute hepatitis and renal failure after an oral dose (112 mg of Subutex) and a report by Brewster of elevated plasma buprenorphine concentrations (80-times higher) in rats after intravenous (IV) administration compared with SL administration.

As a result of the Agency's concerns regarding potential hepatotoxicity of buprenorphine, the Applicant was asked to perform a hepatic safety analysis of all available sources of information, including clinical trials, literature and post-marketing safety reports with submission of NDA 22-410

2.2 Suboxone Post-Marketing Hepatic Safety Study

As a Phase 4 commitment secondary to the approval of Suboxone and Subutex SL tablets, (Study CTN-0027 [START study]) a randomized, open-label, parallel group, multicenter study is currently ongoing comparing Suboxone SL tablets and methadone on indices of hepatic safety.

[2] Berson A, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. J. hepatol 2001; 34:346-350

A secondary objective of the study includes identifying risk factors at baseline and during treatment that could contribute to interactions with Suboxone SL tablets or methadone causing liver dysfunction.

As of August 26, 2008, there were 1,277 subjects who had consented for the study. Of these, 460 were randomized to treatment with Suboxone and 388 to methadone. Specific hepatic data from this study were not provided for review at this time. Table 1 below summarizes the safety findings to date.

Table 1: Summary of Safety Findings in Study CTN-0027 (as of August 26, 2008)

	Suboxone SL Tablets N=448*	**Methadone N=385***	**All N=833***
Any adverse events			
Number of events	1166	1378	2544
Number of subjects with events	285 (63.6%)	297 (77.1%)	582 (69.9%)
Related adverse events			
Number of events	322	351	673
Number of subjects with events	148 (33.0%)	143 (37.1%)	291 (34.9%)
SAEs			
Number of events	14	46	60
Number of subjects with events	12 (2.7%)	32 (8.3%)	44 (5.3%)
Related SAEs			
Number of events	3	8	11
Number of subjects with events	3 (0.7%)	8 (2.1%)	11 (1.3%)
Number of subjects who discontinued due to an adverse event	2 (0.4%)	1 (0.3%)	3 (0.4%)
Number of subjects who discontinued due to an SAE	0	1 (0.3%)	1 (0.1%)

Abbreviation: SAE = serious adverse event.
* Number of subjects who received at least one dose of study drug (i.e., safety population).
Data on file at Reckitt Benckiser.

(Source: Applicant's 4 month Safety Update, p. 237)

At Agency request, in absence of results from the post-marketing study, Reckitt Benckiser compiled information relevant to the hepatic safety of buprenorphine for consideration as part of this NDA.

2.3 Material Reviewed

To determine whether there is any new information regarding the effect of buprenorphine on the liver that would warrant a change to the proposed labeling, the following data were reviewed:

- Reckitt-Benckiser Responses to the Division of Anesthesia, Analgesia and Rheumatology (DAARP) questions of March 16, 2009 provided in the Applicant's document dated April 6, 2009 (Amendment 0012) which included the following:
    - Published literature review summaries pertaining to Buprenorphine and Hepatoxicity
    - Hepatic Adverse Events in Unpublished Reckitt Benckiser Clinical Trials
        - Nineteen (19) Phase 1 PK Studies
        - Phase 2 Studies (Study RB-US-07-0001 and Study RB-US-07-0002)
    - Hepatic Adverse Events in Post-marketing Pharmacovigilance
        - Subutex SL tablets (cumulative 1/1/1997 – 10/31/08)
        - Suboxone SL tablets **(**cumulative 1/1/03 – 10/31/08)
        - (Other) Buprenorphine (cumulative 1/1/05 – 10/31/08). Other buprenorphine includes the following:
            - Temgesic®, Buprex®, and Lepetan® (which are not marketed in the US)
            - Buprenex® (marketed in US approved for analgesia)
- Pertinent sections of the NDA Submission electronically submitted via Global Submit
- Information request responses from the Applicant sent to the Agency
- Medical Officer (MO) Review submitted by James Kaiser, MD, Office of Surveillance and Epidemiology (OSE) dated 5/15/09 on Buprenorphine-related hepatic Toxicity

2.3.1 Published literature reviews pertaining to Buprenorphine and Hepatoxicity

The Applicant's final summarized analyses were of 6 studies in the published literature which contain information pertaining to buprenorphine-related hepatotoxicity in clinical trials and which they submitted in Amendment 0012. They previously reviewed several articles presented with the initial submission. However, they subsequently excluded some of those articles (Zuin, Herve, and Jones) because the individual case report data from those studies were included in their postmarketing database. The Applicant removed an article by Dugarin because it was not a report of a hepatic related AE. An

article by Bruce was removed because the Applicant's primary purpose was to review studies which showed changes (specifically worsening) of hepatic enzymes. The Bruce article did not report any LFT abnormalities. Brief summaries of these articles are included in this review for purposes of completeness after the discussion of the articles included in the Applicant's analysis.

(Study 1) Reference/Title: Lofwall MR, Stitzer ML, Bigelow GE, Strain EC. Comparative safety and side effect profiles of buprenorphine and methadone in the outpatient treatment of opioid dependence. Addict Disorder Therapeutic Treatment 2005; 4:49-64.

Objectives: To present the comparative safety and side effect profiles of buprenorphine and methadone, including gender relationships, from a clinical trial comparing buprenorphine and methadone in the outpatient treatment of opioid dependence

Methods: One hundred sixty four opioid-dependent volunteers age 18-50 years were randomized to buprenorphine sublingual solution (n=84) or to methadone (n=80) for 16 weeks of maintenance. Liver function tests, vital signs, patient self-reports of common medication side effects, and medical reports of adverse effects were assessed.

Hepatic Results: As can be seen in Table 2 below, **t**here were 39.6% of buprenorphine subjects who experienced an increase in ALT (SGPT) from normal baseline compared to 26.2% of methadone subjects. Changes in AST (SGOT) occurred in 39.5% of buprenorphine subjects and 27.5% of methadone subjects. More methadone subjects (45.5%) had abnormal SGOT values become normalized while on methadone than did those on buprenorphine (28.6%).

Table 2: Percent of Subjects with Change in Abnormal Liver Function Tests

LFT Analyte	# Subjects Change in LFT Normal to Abnormal		# Subjects Change in LFT Abnormal to Normal	
	Buprenorphine	Methadone	Buprenorphine	Methadone
SGOT	19/48 (39.6%)	11/42 (26.2%)	2/7 (28.6%)	5/11 (45.5%)
SGPT	17/43 (39.5%)	11/40 (27.5%)	4/13 (30.8%)	3/12 (25.0%)

(Source: Table prepared by reviewer from text of Lofwall article referenced above)

Impression: This study demonstrates that fluctuations between normal and abnormal are quite common in this population, but suggests that buprenorphine-treated patients may be more likely to develop new abnormalities and less likely to have existing abnormalities normalize than patients treated with methadone.

This article addressed hepatic findings comparing buprenorphine to methadone. The duration of the study allows for a better determination of the effect of buprenorphine on hepatic enzymes over time.

Study Limitation: The small sample size could have limited the power to detect significant differences between the two medications.

(Study 2) Reference/Title: Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. J Subst Abuse Treat 2004; 27:75–82.

Objectives: To evaluate the efficacy of administration of high doses of buprenorphine during 24 hour in the management of acute opioid withdrawal

Methods: 40 subjects were enrolled (20 in experimental high dose and 20 in conventional group). Thirty-six subjects completed the trial which consisted of comparing a 24-hour detoxification (12 mg buprenorphine IM in 24 hrs) versus detoxification using a dose tapered over 5 days with starting dose of 3 mg buprenorphine.

Hepatic Findings: The 5-day treatment group ALT levels showed a mean± SD from baseline of 17.44 ± 22.10 U/L. The 24-hour treatment group ALT levels showed a mean± SD from baseline of -2.47 ± 24.34 U/L.

In the experimental group, 1 patient had an ALT level above the upper limit of normal (ULN) at baseline but no patients had an ALT above the ULN at the end of study. No patients had an AST level above the ULN at baseline but 5 patients had AST elevations at the end of the study.

In the conventional group, 2 patients had ALT levels above the ULN at baseline and 5 patients had ALT levels above ULN at the end of the study. ALTs never exceeded 2X the ULN. One patient had elevated AST at the beginning of the study and 8 patients had

elevated AST levels at the end of the study. The AST of one patient in the conventional group exceeded 2X ULN.

Reviewer Impression: This study suggests that treatment-emergent elevations in hepatic enzymes may be more common with five days of buprenorphine treatment than with 24 hours of dosing, despite the higher total daily dose in the 24-hour treatment group.

Limitations:

- Patients were allowed to receive concomitant medications (Indomethacin, trazodone, chlorpromazine, hyoscine and diazepam) which may have affected LFTs
- No actual raw data (hepatic laboratory values) were listed in the study
- Study compared buprenorphine to buprenorphine

(Study 3) Reference/Title: Sullivan LE, Barry D, Moore BA, Chawarski MC, Tetrault JM, Pantalon MV,O'Connor PG, Schottenfeld RS, Fiellin DA. A trial of integrated buprenorphine/naloxone and HIV Clinical Care . Clinical Infect Dis 2006 Dec 15;43 Suppl 4:S184-S190.

Objectives: To investigate the feasibility (safety) and efficacy of integrating buprenorphine, along with 2 levels of counseling, into HIV clinical care

Methods: A 12 week pilot study which evaluated safety and efficacy of buprenorphine/naloxone in 16 HIV patients. The study was conducted in an outpatient clinic. Buprenorphine was provided as buprenorphine/naloxone (4:1) in a sublingual tablet. Patients received 8 mg (buprenorphine component) on day 1, 12 mg on day 2, and 16 mg thereafter. The dosing protocol allowed for 2 dose upgrades (to 20 mg and 24 mg). The dose of buprenorphine/naloxone was increased when urine toxicology results continued to be positive for opioids or when patient discomfort resulted from withdrawal or opioid craving. There was a 2 week stabilization phase, 10 week maintenance phase and an optional 2 week buprenorphine/naloxone taper or to continue in a compassionate-use extension phase.

Hepatic Findings: Thirteen patients completed 12 weeks of treatment. Ten of these 13 patients had antibodies to HCV. The authors of the article report that there were no significant changes in ALT or AST during the course of the study. The mean ALT level (±SD) was 39.8± 18.1 U/L at baseline and 43.0 ± 29.4 U/L at month three. The mean AST levels (±SD) were 36.5 ± 16.0 and 39.2 ± 23.4 U/L, respectively.

Study Limitation: The study was not designed to assess the effect of buprenorphine on hepatic enzymes. No specific laboratory values were given in the article.

Reviewer Impression: No specific conclusion can be drawn as there is limited information in the article regarding hepatic enzymes. The study was conducted in an outpatient setting so it is difficult to control for confounders.

Summary of Other Studies Reviewed:

- McCance-Katz EF, Moody DE, Morse GD, Friedland G, Pade P, Baker J, et al.Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside Reverse-transcriptase inhibitors efavirenz and delavirdine. Clin Infect Dis 2006a;43(4):S224-S234

- McCance-Katz EF, Moody DE, Smith PF, Morse GD, Friedland G, Pade P, et al. Interactions between buprenorphine and antiretrovirals II. The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. Clin Infect Dis 2006b;43:S235-S246.

- McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend 2007;91:269-278.

  The three above studies authored by McCance-Katz, et al were analyzed by the Applicant in the submission. However, these studies were designed to address drug/drug interaction of various antiretrovirals in patients maintained on buprenorphine. The design of these studies does not shed light on the issue of buprenorphine-induced hepatic effects so they were not discussed in detail in this review.

- *Bruce RD, Altice FL. Case series on the safe use of buprenorphine/naloxone individuals with acute hepatitis C infection and abnormal hepatic liver transaminases. Am J Drug Alcohol Abuse 2007;33:869-874*. A case series which interviewed buprenorphine injectors in Malaysia. No clinical information pertaining to hepatic enzymes was reported. (Study was not included in the final analysis)

- *Herve, S., et al. Acute hepatitis due to buprenorphine administration. European Journal of Gastroenterology & Hepatology, Vol. 16, N0 10, 2004.* Seven case reports of acute cytolytic hepatitis due to buprenorphine. All patients had anti-HCV positive serology and two had positive HCV-RNA. Two patients were hepatitis B surface antigen (HbsAg) carriers. The diagnosis of buprenorpohine-induced hepatitis was considered probable. (Applicant reports that these findings are captured in the postmarketing data)

- *Zuin M. et al. Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. Dig Liver Disorder 2008 Feb 20; 1-3*. A case of acute liver and kidney failure in a patient with latent HCV following buprenorphine was reported. Histology did not confirm HCV reactivation or liver cirrhosis. Liver and kidney failure resolved after buprenorphine was discontinued. (Applicant reports that these findings are captured in the postmarketing data)

- *Dugarin, J. et al. Opiate substitution. Concours Medical 2005; 127(37):2113-2114.* A case of an HIV positive patient taking buprenorphine and antiretroviral therapy who developed hepatits C was reported. The Applicant reports that this was not considered a buprenorphine related AE and data from this study was not included in the final analysis.

- *Noblet, C. et al. Liver Injury caused by high dosage buprenorphine (HDB, Subutex): a national investigation by the French pharmacovigilance system (Abstract). Fundam Clin Pharmacology 2002; 16:417.* The applicant described, but did not submit, this abstract. A literature search by this reviewer did not find the article. The Applicant's description of this article in their original submission reads "Very brief details have been published of a review in 2002 by the French pharmacovigilance system which found that high dose buprenorphine caused liver damage in 30 patients". Data from this article was not included in the Applicant's final analysis.

Reviewer Discussion: The Applicant presented literature representing hepatic data from 197 subjects who were exposed to buprenorphine in their final review analysis. The maximum duration of exposure was 26 weeks (Lofwall article). The population was heterogeneous. Only one study (Lofwall) compared buprenorphine to methadone. The Applicant reported that a total of 54 LFT assessments among buprenorphine treated subjects changed from normal to abnormal during these studies out of a total of 236 assessments (22.9%), with more LFT assessments changing from normal to abnormal in the study by Lofwall. No clear patterns emerged.

2.3.1.1 *Reviewer Comments (Hepatic Literature Review):*

Due to the variability in study designs and confounding variables (such as subjects with HCV, HBV and/or HIV, IVDU and/or ethanol abuse, as well as concomitant medications) no definitive conclusions can be drawn regarding any trends for hepatotoxicity and buprenorphine based upon the literature reviewed. Buprenorphine appears to have a causative or contributory role in the development of hepatic abnormality in some cases, but no definitive causality can be concluded based on the literature reviewed. (The reader is referred to Dr. James Kaiser's OSE review for additional comments regarding buprenorphine and hepatotoxicity literature review).

2.3.2 Hepatic Adverse Events in Suboxone (b) (4) Clinical Trials

2.3.2.1 Phase 1 PK Studies

Nineteen Phase 1 cross-over studies were conducted in healthy volunteers. Six hundred twenty three (623) subjects received at least one dose of a product containing buprenorphine.

There were no deaths or hepatic-related SAEs. One subject experienced a hepatic adverse whose narrative is provided below.

> **Narrative - Subject 645 (Liver enzyme elevation):** This subject was a 33-year-old White female with no significant medical history. She received naltrexone for Period 1 on August 4, August 5 (2 doses), and August 6, 2008, and received buprenorphine/naloxone soluble film 12 mg/3 mg via sublingual administration on August 5, 2008. She received naltrexone for Period 2 on August 18, August 19 (2 doses), and August 20, 2008 and Suboxone tablets on August 19, 2008. The subject was discontinued from the study due to missing her Period 3 check-in appointment. Laboratory values were drawn during the discharge visit on September 8, 2008 (19 days after the previous dose of naltrexone and 20 days after the dose of Suboxone) and revealed
>
> - ALT elevated to 107 U/L (screening ALT was 14 U/L),
> - AST elevated to 309 U/L (9 times the upper limit of normal, screening AST was 19 U/L), and
> - LDH elevated to 542 U/L (screening value was 197 U/L).
> - Total bilirubin was normal at 0.3 mg/dL.
>
> A repeat laboratory assessment was performed on September 10, 2008, and ALT was 71 U/L, AST was 96 U/L, and LDH was 345 U/L. No additional treatment was administered. It is not known if the abnormalities resolved. No further evaluation or follow-up was reported.

2.3.2.2 Phase 2 Clinical Studies (RB-US-07-0001 and RB-US-07-0002)

There were no deaths or SAEs related to hepatic toxicity reported in either of the Phase 2 clinical studies. In addition, there were no cases of liver failure, no drop outs or discontinuations due to hepatic associated findings and no Hy's Law cases. There was one hepatic-related AE in study RB-US-07-0002 (Subject # 128) and one subject with clinically significant elevated hepatic enzymes (Subject #101). These subjects are discussed in further detail under the discussion of Study RB-US-07-0002 below.

In Study RB-US-07-0001, an open-label 12-week safety study, liver function tests were not assayed. The Applicant reports that no hepatic-related AEs were reported.

Study RB-US-07-0002 was a Phase 2, double-blind, randomized study conducted in a supervised residential unit on healthy adult male and female subjects with opioid dependence. The study included a morphine maintenance period (Study Days 1-6) and a Buprenorphine Film (b) (4) Induction and Post Induction period (Study Days 7-11).

A total of 49 subjects entered the morphine maintenance phase. Ten subjects were not randomized to treatment with buprenorphine or buprenorphine/naloxone films, either because they did not meet criteria for being able to detect withdrawal during the naloxone challenge session or for other reasons. One subject who was randomized withdrew before receiving buprenorphine. Therefore, there were a total of 38 randomized subjects (20 received buprenorphine soluble film (Group A) and 18 received buprenorphine/naloxone soluble film (Group B)). There were 34 evaluable subjects (18 received buprenorphine soluble film and 16 received buprenorphine/naloxone soluble film). Evaluable subjects were defined as those who completed the study through the first two days of soluble film administration and had assessments for 23.5 hours after the first day of soluble film administration.

Most subjects who received randomized treatment were male (75.0% buprenorphine and 61.1% buprenorphine/naloxone) and either white (60.0% and 72.25, respectively) or African American (40.0% and 22.2%, respectively). The mean age of both randomized treatment groups was 40.2 years.

Viral hepatitis was the most common medical condition (experienced by ≥ 5%) of subjects (15.8% hepatitis C and 2.6% hepatitis B).

There were ten (10) evaluable subjects who received morphine but did not receive buprenorphine. For purposes of data analysis, this untreated group serves as a comparison group for hepatic findings.

A total of 8 subjects experienced liver function elevations in Group A(buprenorphine), 4 in Group B (buprenorphine/naloxone) and 5 in the Untreated Group as shown in Table 3 below. Each number in the column represents a single patient and the categories are mutually exclusive.

Table 3. Subjects with Treatment-emergent elevations in hepatic enzymes Study RB-US-07-002

Analyte	Group A (Buprenorphine) N=18	(%)	Group B (Suboxone) N=16	(%)	Untreated (Morphine only) N=10	(%)
ALT + AST	4	(22)	2	(12)	2	(20)
ALT	2	(11)	1	(6)	-	
AST	-		-		-	
AP	2	(11)	-		1	(10)
ALT +AST+ AP	-		1	(6)	-	
AST + AP	-		-		-	
Total	8	(44)	4	(25)	3	(30)

AP = alkaline phosphatase
(Source: Table prepared by reviewer from data provided by Applicant's Study Report)

The results were further categorized according to whether hepatic enzymes worsened from a normal baseline or worsened from an already elevated baseline. A baseline change of 10% was considered significant for purposes of this review to analyze data. These findings are shown below in Table 4. Appendix 1 gives a detailed analysis of each subject and the exact values of the hepatic analyte.

Table 4. Type of Hepatic Change Experienced by Subjects (Study RB-US-07-002)

ALT	Group A (Buprenorphine) N=18	(%)	Group B (Suboxone) N=16	(%)	Untreated (Morphine only) N=10	(%)
Any worsening	6	(33)	4	(25)	2	(20)
Normal to abnormal	5	(28)	3	(19)	1	(10)
Abnormal to worsened	1	(5)	1	(6)	1	(10)
AST						
Any worsening	4	(22)	3	(19)	2	(20)
Normal to abnormal	2	(11)	1	(6)	1	(10)
Abnormal to worsened	2	(11)	2	(13)	1	
AP						
Any worsening	2	(11)	1	(6)	1	(10)
Normal to abnormal	1	(6)	1	(6)	-	
Abnormal to worsened	1	(6)	-		1	(10)

(Source: Table prepared by reviewer from data provided by Applicant's Study Report)

The measures of central tendency for AST, ALT, and total bilirubin the Study RB-US-07-0002 are shown in table 5 below.

Table 5. Measures of central tendency for Hepatic Enzymes (Study RB-US-07-0002)

	Soluble Film Treatment Group					
	Buprenorphine (N=19)[a]			Buprenorphine and Naloxone (N=16)[a]		
	Baseline	Post-test	Change[b]	Baseline	Post-test	Change[b]
ALT; normal range 9-80 U/L (males) and 6-40 U/L (females)						
Mean	27.1	47.7	20.7	38.8	57.3	18.4
SD	22.15	41.26	29.67	40.13	58.01	41.24
Median	17.0	32.0	9.0	23.0	31.0	8.5
Min, Max	6, 91	9, 160	-8, 98	9, 160	9, 211	-48, 147
AST; normal range 10-40 U/L (males 20-49 years), 10-35 U/L (males ≥50 years), 10-30 U/L (females 20-44 years), and 10-35 U/L (females ≥45 years)						
Mean	27.8	35.5	7.7	34.6	41.7	7.1
SD	19.94	26.83	17.84	21.19	33.89	32.22
Median	20.0	26.0	3.0	24.0	28.5	2.5
Range	13, 98	12, 119	-12, 69	15, 71	15, 128	-46, 109
Total bilirubin; normal range 0.2-1.2 mg/dL						
Mean	0.59	0.53	-0.06	0.63	0.61	-0.03
SD	0.200	0.267	0.269	0.149	0.214	0.257
Median	0.60	0.50	-0.10	0.60	0.60	0.00
Range	0.3, 1.0	0.3, 1.2	-0.6, 0.6	0.4, 0.9	0.3, 1.0	-0.5, 0.4
Alkaline phosphatase; normal range 40-115 U/L (males), 33-115 U/L (females 20-49 years), and 33-130 U/L (females ≥50 years)						
Mean	68.2	77.1	8.9	81.2	80.8	-0.4
SD	24.88	24.03	24.44	25.31	21.90	18.94
Median	68.0	76.0	6.0	80.0	74.5	-1.5
Range	10, 118	48, 136	-32, 68	54, 154	48, 127	-48, 43

(Note: Applicant's normal range of ALT is upper limit 60 U/L not 80 U/L as shown. Applicant reported typographical error. Corrected table to be submitted but pending at the time of this review. Does not change raw data as reported in table) (Source: Applicant's 4 Month Safety Update, p. 146)

Most changes recorded were regarded as not clinically significant. However, two of 38 subjects (both treated with buprenorphine/naloxone) developed clinically significant changes in hepatic enzymes during the five days of treatment. Brief narratives are provided on those subjects below:

Narrative - Subject 101(Suboxone treated arm) was a 26 year-old male who reported a history of hepatitis C, had elevated ALT (160 U/L) and AST (71 U/L) during screening but these elevations were not considered to be clinically significant or exclusionary for study participation.

He was randomized to buprenorphine/naloxone soluble films and received all 5 days of administration. At discharge, ALT was elevated to 226 U/L (AST appears not to have been documented). At an extra follow-up visit 10 days later, ALT was 211 U/L and ALT was elevated at 105 U/L.

Narrative - Subject 128 (Suboxone treated arm) was a 47 year-old female who reported "having a possible history of hepatitis B" had normal ALT and Alk Phos at baseline, but a baseline AST value of 37 U/L which was considered not clinically significant. She was randomized to buprenorphine/naloxone soluble films and received all 5 days of administration. At discharge, lab values were ALT 167 U/L; AST 128 U/L; and Alk. Phos. 127 U/L, all of which were considered clinically significant abnormalities.

Of the subjects with treatment-emergent abnormal ALT or AST values, three had a history of hepatitis (Subject #'s 101 and 128 were in the Suboxone treated arm as discussed above and Subject 116 was in the buprenorphine treated arm. The applicant reported that 7 subjects were receiving concomitant medications which included ibuprofen, ibuprofen plus acetaminophen, acetaminophen, and ciprofloxacin plus acetaminophen with codeine.

Discussion: Suboxone (Buprenorphine + Naloxone) had fewer subjects who experienced elevated hepatic enzymes during this study. The analytes most frequently involved were an ALT and AST combination. In those subjects with elevations of hepatic enzymes, most levels increased from normal to abnormal, suggesting that Buprenorphine may play a causative role in increasing liver enzymes. However, it is noted that thirty percent of the untreated (Morphine) group also experienced liver function elevations (greater than the buprenorphine/naloxone group).

Conclusion:

- Subjects on Suboxone experienced fewer cases of elevated hepatic enzymes
- Of those subjects who had elevated hepatic levels, most experienced a change from normal to elevated levels
- The most common hepatic enzyme elevation was the combination of ALT and AST in both Buprenorphine and Suboxone groups
- AST appeared more likely to worsen if the level was already elevated at baseline
- Treatment-emergent ALT values ranged from 41 U/L to 167 U/L
- Treatment-emergent AST values ranged from 36 U/L to 128 U/L

2.3.2.3 *Reviewer Comments (Hepatic Clinical Studies):*

Some degree of fluctuation in hepatic enzymes may be typical in this population.

2.3.3 Hepatic Adverse Events in Post-marketing Pharmacovigilance

2.3.3.1 Hepatic-Related Deaths:

The Applicant reported ten (10) buprenorphine-associated hepatic deaths since the initial marketing of Subutex.

Patients who received both Suboxone and Subutex were classified to the first reported drug for the adverse event. Six of the ten cases involved Subutex as the first buprenorphine product listed and 4 involved Suboxone as the first buprenorphine product listed.

The full hepatic death narratives for these subjects were provided by the Applicant and were reviewed.

This reviewer found that there were 2 possible buprenorphine-related cases (PR/97040402/120 and RB-1290-2005) 2 unlikely cases (PW/020827/445 and RB-11823-2004) and the remaining 5 with incomplete information. In most cases where adequate information was available, there were confounding factors which made it difficult to determine whether buprenorphine was the most likely cause for death.

Therefore, in this review, no death definitely caused by buprenorphine was found based upon the post marketing data submitted by the Applicant. The reader is referred to the OSE Review of Dr. James Kaiser for additional information regarding AERS data review.

A summarized version of the hepatic death narratives with reviewer comments is shown in Table 6 below:

Table 6: Narrative Summaries Buprenorphine-related Hepatic Deaths
*(One case of suicide has been omitted from the table below because the death was not related to hepatic events)

ID # **Narrative Summary**	**Confounders**	**Reviewer Comments**
Subutex (Hepatic Deaths)		
JP/980114/475 31 yo male received Subutex SL 10 mg daily from 3/2/1996 until an unknown date. Medical history was notable for hepatic cirrhosis, HCV and HIV. In (b) (6) (date not specified) the patient died. The death was attributed to aggravation of hepatic cirrhosis leading to **liver failure.** The relationship of the death to Subutex was not determined.	Hepatic cirrhosis, HCV, HIV	Incomplete information; can not determine causality
PR/970401/116 32 yo male received Subutex 4 mg/day SL for 19 weeks (3/20/96 to 8/1/96). Patient died in (b) (6) reportedly due to aggravation of **hepatic cirrhosis.**	Hepatic cirrhosis, (+) HBV, HCV, HIV	Incomplete information; can not determine causality
PR/970402/120 33 yo male received Subutex SL 2 mg daily starting on 3/31/96. Patient intentionally misused the product via IV and exceeded the prescribed dose (injecting 8 mg four to eight times per day). Hospitalized (b) (6) for hepatitis and anicteric cholestasis. Patient was discharged on (b) (6) and Subutex was resumed on 6/19/96. On (b) (6) the patient was readmitted to the hospital for hepatitis, asthenia and icterus. Subutex was discontinued on 6/27/96. On (b) (6), the patient died from **hepatocellular insufficiency.**	(+) HCV, HIV Concomitant meds: Fluconazole, trimethoprim, sulfamethoxazole, amoxicillin Chronic IV use of Subutex	Possible causality, multiple confounders
PW/020827/445 80 yo female received a buprenorphine injection (Temgesic) at an unknown dose on 3/21/01. Medical history was notable for hypertension and rheumatoid arthritis. She was treated with methotrexate until 3/13/2001. On (b) (6) she fell and sustained a femoral neck fracture. On (b) (6) she received the Temgesic injection prior to surgery. She also received unknown dosages of cefazolin for antimicrobial prophylaxis and metoclopramide. On (b) (6) the patient experienced abdominal pains and	Concomitant pre-op medications: IV ketoprofen; cefazolin	Unlikely causality

hemodynamic instability. Later that evening she went into cardiogenic shock with acute pancreatitis. On (b) (6) she experienced acute renal failure and **acute hepatic failure**, and died.		
RB-1183-2004 36 yo male received Subutex 8 mg oral from an unknown date until 10/1/04. Medical history was significant for HCV and hepatic cirrhosis (advanced stage), AIDS, alcohol and drug abuse, hepatic encephalopathy and cerebral toxoplasmosis with epilepsy and hemiparesis. The patient was on multiple medications for multiple medical conditions. Subutex was discontinued on 10/1/04. The patient died on (b) (6) with diagnosis of acute decompensation of **hepatic insufficiency**.	Concomitant medications: peginterferon alfa-2B, ribaririn, gabapentin, lopinavir/ritonavir and zidovudine/lamivudine, pentamidine isothionate, furosemide and spironolactone, clarithromycin and minocycline.	Unlikely causality; Multiple confounders (medications and multiple life-threatening medical conditions all of which could have contributed to patient's death)
RB-1290-2005 24 yo male received Subutex 16 mg daily from 2/26/04 to 9/18/04. Medical history significant for HCV, drug abuse, and liver rupture following a motorcycle accident. On (b) (6) patient was hospitalized with back pain, elevated ALT, jaundice. Patient received 20 mg piroxicam daily for back pain beginning 9/16/04. He was hospitalized on (b) (6) with elevated ALT. He died on (b) (6) due to **liver cirrhosis, liver failure** and esophageal varices.	Concomitant medications: Piroxicam	Possible causality; but traumatic liver rupture could have been underlying etiology for liver failure.
Suboxone (Hepatic Deaths)		
RB-4329-2006 Female (of unknown age) who received Suboxone 6 mg SL tablets on an unknown date. Medical history was unknown. Immediately following Suboxone administration the patient began experiencing nausea and convulsions. She was treated with an unknown dose of Promethazine and 0.3 mg buprenorphine injection before being taken to the ER. A follow up telephone call reportedly confirmed that the patient experienced **liver toxicity** as a result of pancreatic cancer and died. The cause of death and the timeline corresponding to the events are unknown.	Pancreatic cancer	Incomplete information; can not determine causality

RB-8290-2007 Pregnant female of unknown age who received Suboxone at an unknown dose prior to her pregnancy and was switched to Subutex at an unknown dose on an unknown date. She reportedly had a history of fatty liver of pregnancy. She went into l**iver failure** at an unknown time during her pregnancy and delivered a stillborn infant. She remained in the ICU, developed aspiration pneumonia and died shortly thereafter.	Fatty liver of pregnancy	Incomplete information; can not determine causality
RB-8760-2007 25 yo male received unknown dosage of Suboxone for an unspecified duration. No medical history available. Patient died in (b) (6) of cardiac arrest. Was also noted to have **AST/ALT > 1000 U/L** and CPK elevated. The patient had ingested Suboxone in 2007.	Three substances were noted at autopsy, the details of which are unknown.	Incomplete information; can not determine causality

2.3.3.2 Postmarketing Hepatic-Related SAEs:

The Applicant's initial submission and 4-month Safety Update noted that of 563 hepatic adverse events reported, 308 (55%) were reported as serious. However, upon further review of their data and performing an internal analysis of hepatic safety, they revised the number of hepatic AEs. This revised number was the result of deleting reported cases of non-hepatic induced pruritus, non-hepatic induced coagulopathy and erroneously coded reports. The revised number of SAEs was not provided for the final revised data but they did report that 227 patients experienced hepatic AEs.

There were 18 hepatic SAE narratives provided by the Applicant. The full narratives for hepatic SAE subjects were reviewed by this reviewer. A summarized version of the hepatic SAE narratives with reviewer comments is shown in Table 7 below:

Based upon this review, there were three probable cases (RB-402-2004; RB-1596-2005 and RB-2136-2005) ; 10 possible cases (RB-1335-2005; RB-4821-2007; RB-5522-2007; RB-1455-2005, RB-420-2004, RB-402-2004, PR/990608; RB-2449-2005, RB-959-2004; RB-3256-2006; RB-3345-2006); 4 incomplete information (PR/970507/189 ; RB-5639-2007; RB-3341-2006; and RB-4090-2006) and 1 unlikely (RB-318-2003) case of buprenorphine causality in the hepatic SAEs. The possible cases, however, are confounded by multiple concomitant medications or complex medical history which made it difficult to isolate buprenorphine causality.

Table 7 . Tabular Summaries of Hepatic Serious Adverse Events

ID # **SAE Narrative Summary**	**Confounders**	**Reviewer Comments**
PR/970507/189 **Hepatic Failure** Newborn infant born (b) (6) to a mother of unknown age who had been treated with Subutex for unknown dosage and unknown duration. Soon after birth, the infant exhibited hepatic dysfunction and hyperammonemia and was diagnosed with hepatic failure. No further information is available.	No additional information available No other medical history provided.	Incomplete information; can not determine causality
RB-1335-2005 **Acute hepatic failure** 65 yo male received Lepetan injection (buprenorphine HCL 0.9 mg/day) IV for chest pain from (b) (6) for chest pain. Diabetes history. On (b) (6) was hospitalized for acute inferior wall MI. On (b) (6) he experienced complete AV block with circulatory collapse and acute renal failure. On (b) (6) he experienced acute liver failure. Hepatic enzymes (AST 2916 IU/L, ALT 1258 IU/L). Lepetan was discontinued same day but patient had no immediate change in LFTs. He required plasma exchange. Cardiac function improved with ongoing medical management. On (b) (6), the LFT results had improved (AST 620 IU/L, ALT 347 IU/L and LDH 670 IU/L). Hepatic function normalized with over next 2-4 weeks.	Probable ischemic hepatitis due to circulatory collapse	Possible causality

Table 7 (cont'd)

ID # SAE Narrative Summary	Confounders	Reviewer Comments
RB-4821-2007 **Acute hepatic failure** 41 yo male received 8 mg Suboxone tablets 3 time per day (total dose 24 mg/day) sublingually from October 20, 2006 to October 30, 2006. Was hospitalized on unknown date for hepatic failure. The patient was discharged, and as of (b) (6) was considered to be recovering from acute liver failure	Subject had also been taking up to 6 g of acetaminophen per day for pain and 3 Suboxone tablets per day (32 mg/day)	Possible causality; Confounder of concomitant medication (acetaminophen)
RB-5522-2007 **Acute liver failure** 20 yo female taking 16 mg Suboxone once daily from February 2, 2007 to March 9, 2007. Acute liver failure onse (b) (6) Liver biopsy showed acute on chronic liver failure. All hepatitis panels were negative.patient was also being treated with ciprofloxacin for pyelonephritis. She apparentlyl started the ciprofloxacin on (b) (6) after presenting to the emergency room with vomiting and (+) urinalysis. As of 5/2/07 her liver function data had normalized. The levels of LFTs were not included in the narrative.	Concomitant medication: ciprofloxacin	Possible causality; Can not rule out ciprofloxacin as cause of liver failure
RB-5639-2007 **Acute hepatic failure** Male, unknown age, unknown dosage of Suboxone daily. Patient had also been taking APAP daily. On an unknown date in (b) (6), the patient was taken to the hospital and diagnosed with acute hepatic failure. His AST/ALT levels were greater than 10,000. The outcome of the event was unknown. No further information available.	Concomitant medication: APAP 4-5 g per day.	Incomplete information; can not determine causality

Table 7 . Tabular Summaries of Hepatic Serious Adverse Events (cont'd)

RB-1455-2005 **Fulminant hepatitis** 31 yo male received 16 mg Subutex daily SL for several months up to March, 1998. Heroin use until 1997. (+) HIV and HCV. On (b) (6) hospitalized with asterixis. For 3 days prior to hospitalization, he had taken a total of 5 g paracetamol and 2 g ASA orally for unknown indication. LFTs were elevated with ALT 6595, AST 2831, GGT 168, Alkaline phosphatase 306 and total serum bilirubin was 192 umol/L. A liver biopsy rvealed panlobular necrosis and mononuclear cell inflammatory infiltrate. All medications were interrupted and patient quickly improved.	(+)HIV; (+)HCV APAP 5 g daily and Aspirin 2 g daily x 3 days prior to onset	Possible causality; Confounder of concomitant medication
RB-402-2004 **Hepatorenal failure** 33 yo male received 8 mg Subutex tablets SL daily from 1996 to May 15, 1998. On (b) (6) ingested 112 mg Subutex leading to hospitalization and a diagnosis of cholestasis associated with severe cytolytic syndrome. Excessive buprenorphine (224 ng/ml) and norbuprenorphine (30 ng/mL). Paracetamol level was not toxic (3.6 mg/L). Once Subutex was discontinued, almost complete normalization of hepatic results.	Multiple concomitant medications:s (Bromazepam, Zopiclone, Paracetamol, Codeine)	Probable causality; symptoms improved when Subutex was discontinued
RB-420-2004 **Acute hepatocellular failure** and acute oliguric renal failure. 19 yo male, Unknown dosage of Subutex SL for unknown duration; psychiatric disorders. Found unconscious and in coma on (b) (6). Subutex intoxication suspected as 2 empty tablets of the medication were found near the patient. Plasma levels were < 1 g/L. Toxicology showed traces of antidepressives and (+) benzodiazepines.	Multiple concomitant meds (Flupentixol, tropatepine, clorazepate, zoplicone, olanzepine)	Possible causality (overdosage) ; concomitant toxicology of benzodiazepines
PR/990608/150	(+) HIV, (+) viral	Possible causality;

Hepatic encephalopathy 35 yo male received Subutex 8 mg SL daily Oct 8, 1998 for 7 months. Multiple medical conditions to include HIV, viral hepatitis, drug abuse (morphine), epilepsy and tuberculosis. Hospitalized (b) (6) with hepatic encephalopathy. Had been on isoniazid and rifampin for tuberculosis. On 10/12/98 isoniazid and rifampin were discontinued and hepatic enzymes improved. Subutex was not discontinued. On (b) (6) a liver biopsy confirmed hepatic cirrhosis with morphologic signs of chronic cholestasis associated with lesions of acute cholantiolitis and portal granulomas. Hepatic enzymes were still elevated on 11/26/98 (levels not given) but clinically patient was doing well	hepatitis Concomitant medications (isoniazid; rifampin)	confounders of concomitant tuberculosis medications
RB-1596-2005 **Hepatic encephalopathy** 18 yo male started Suboxone 12 mg on 4/27/05, then 16 mg daily until 5/4/05 for a cumulative dose of 124 mg. Hospitalized with markedly elevated LFTS from baseline. Baseline LFTs on 4/27/05 were AST 22; ALT 18. On 5/4/05 LFTs were > 700. The reaction resolved after stopping Suboxone	None	Probable causality

RB-2449-2005 **Hepatic encephalopathy** 40 yo male chronic alcohol abuse with probable hepatic cirrhosis. Received Subutex SL since 1996. Treated with Lamivudine/zidovudine in 2004 to treat HIV infection. On (b) (6), hospitalized in ICU for pneumonia. Treated with antibiotics and improved. HIV meds discontinued on 10/17/05. Received Subutex 8 mg orally daily Oct. 16-19, 2005 and from Oct 23-31, 2005 and morphine Oct 20-22, 2005. At admission, diagnosed with hepatomegaly and splenomegaly. Progresive increase of bilirubin (especially conjugated bilirubin) with a peak at 484 uM on 10/30/05. Bactrim IV was started on 10/18/05 but discontinued on 10/24/05. Buprenorphine was discontinued on 10/31/05 as bilirubin continued to increase. Hyperbilirubinemia quickly decreased as buprenorphine was discontinued.	(+) HIV/HCV Concomitant medications (Bactrim, HIV medications)	Possible causality; multiple confounders as noted

Table . Tabular Summaries of Hepatic Serious Adverse Events

RB-959-2004 **Hepatic encephalopathy** 70 yo male, received 0.4 mg Lepetan suppository (buprenorphine HCL) daily rectally from July 2 to July 3, 2003 for relief of pain from a lumbar compression fracture. On (b) (6) he developed encephalopathy. Buprenorphine was discontinued. By July 6, symptoms were improving. Medical history was significant for hepatic cirrhosis, hepatocellular carcinoma and prostate cancer. His concomitant medications included: dexamethasone, digestives, ursodeoxycholic acid, kanamcin sulfate, lactulose, spironalactone, teprenone, ranitidine, omeprazole, and sodium alginate A follow up visit with his physician in October 2004 noted no significant change in the patient's hepatic levels before and after the onset of the hepatic encephalopathy and coma	(+) HCV ; (+) hepatic cirrhosis and hepatocellular carcinoma Multiple concomitant medications Diagnosis of hepatic encephalopathy appears inconsistent with limited medical history provided	Possible causality Buprenorphine was discontinued and symptoms improved. No information was provided as to final outcome
RB-318-2003 **Hepatic encephalopathy** 39 yo female received 2 mg Subutex SL daily from March 12, 2001 to hospitalization (b) (6). Diagnosed with cirrhosis, encephalopathy, and ascites, and galactorrhea with hyperprolactinaemia. Metoclopramide was stopped on 5/26/03 and by (b) (6) the symptoms had disappeared and patient recovered.	Concomitant meds: Spironolactone, furosemide, metoclopramide	Unlikely causality

RB-2136-2005 **Multi-organ failure** 24 yo male started Subutex (dates and dose unknown). Medical history significant for IVDU, pneumothorax and hepatic cirrhosis. Patient intentionally initiated 16 mg Subutex IV by injecting 2 Subutex tablets diluted with tap water. On (b) (6) patient was admitted to ICU for respiratory distress and received mechanical ventilation and dialysis. AST=2192 IU/L; ALT=1373 IU/L; lactase 21 mmol/L. Diagnosed with metabolic acidosis and cirrhotic enlarged liver. Improved symptoms by (b) (6). No further LFT values were reported in the narrative.	None	Probable causality

Table 7 . Tabular Summaries of Hepatic Serious Adverse Events

RB-3256-2006 **Progressive liver failure** 45 yo male received 16 mg Subutex SL daily for unknown period of time; alcohol history and (+) HCV; alcoholic cirrhosis. He presented with decompensated hepatic cirrhosis on an unknown date. The reporting physician determined the event to be medically significant. Upon follow up, it was reported that there were no adverse effects that occurred and question of possible aggravation of pre-existing disorder. No LFT values were listed in the narrative. Final diagnosis was alcoholic cirrhosis and HCV.	Concomitant medications: (Tenoxicam); (+) HCV and alcoholisim	Unlikely causality; confounders as noted
RB-3341-2006 **Progressive liver failure** 66 yo male received Suboxone SL in a taper starting at 12 mg/day on April 3, 2006 down to 0 mg by May 2, 2006 for Oxycontin addiction. Concomitant medications: Metformin, citalopram, atorvastatin, irbesartan/HCTZ, ASA On (b) (6) presented with possible liver failure and elevated ammonia level (68 umol/L) with a negative hepatitis panel and normal liver function tests	Concomitant medications: Metformin, citalopram, atorvastatin, irbesartan/HCTZ, ASA	Incomplete information; can not determine causality
RB-3345-2006 **Progressive liver failure** 56 yo male received Suboxone SL in taper starting at 32 mg daily on 10/4/05. Alcohol use and opioid dependence. Liver failure reported on (b) (6) when Suboxone was started, but physician's report indicates that liver failure started before Suboxone (although a date was not provided in the narrative). Patient was on fentanyl, quetiapine and lactulose.	Conflicting dates for onset of liver failure and Suboxone initiation (+) hepatitis A, HBV, and HCV with chronic elevation of LFTS	Possible causality; multiple confounders; incomplete information

RB-4090-2006 **Progressive liver failure** 37 yo male received Suboxone SL from 1/19/05 to 9/15/06. Doses were tapered from 24 mg to 2 mg daily. Patient last saw physician 7/26/06 (but apparently was prescribed 45 tablets of Suboxone 2 mg on 8/16/06). During this period, the patient was hospitalized (unknown dates) for treatment of jaundice, ascites and fatigue. The physician was told the patient needed a liver transplant. However, the physician had made no contact with the hospital and had no laboratory values. Suboxone was stopped by physician on 9/15/06 but patient was given an additional six 2 mg tablets related to relapse.	The case was ongoing, outcome of liver failure unknown and no further information available.	Incomplete information; can not determine causality

2.3.3.3 Postmarketing Hepatic AEs:

The applicant reported that a total of 227 patients reported hepatic adverse events. They further note that most of the hepatic AEs (126/227 or 55.5%) involve patients who had viral hepatitis, HIV, IVDU and/or ethanol abuse. They report that 33/101 (32.7%) of the other cases involved concomitant use of a hepatotoxic medication or a medication metabolized by the CYP 34 pathway.

In Table 8 below, it can be seen that clinically asymptomatic LFT increase was the most frequently occurring AE at 32% followed by acute hepatitis which occurred in 23% of subjects who experienced hepatic AEs.

Table 8 : Post Marketing Hepatic AEs Buprenorphine

Reckitt Benckiser Internal Diagnosis	Number of Patients
Acute cholestatic hepatitis with hepatomegaly	1
Acute exacerbation of chronic HCV	1
Acute exacerbation of chronic hepatitis	4
Acute hepatitis	53
Acute liver failure	10
Cholangitis	1
Cholestatic hepatitis	19
Chronic hepatitis	4
Exacerbation of pre-existing elevated LFT	7
Fulminant hepatitis with hepatic encephalopathy and hepatorenal syndrome	1
Granulomatous hepatitis	2
Hepatic cyst	1
Hepatic encephalopathy	5
Hepatic encephalopathy with ascites	1
Hepatomegaly	2
Hepatorenal syndrome	3
Hepatosplenomegaly	1
Hyperammonemia	2
Hyperbilirubinemia	1
Icterus	2
Icterus	1
Ischemic hepatitis	4
Jaundice	11
LFT increase - clinically asymptomatic	73
Liver cirrhosis	1
Liver disorder NOS[a]	2
liver necrosis NOS[a]	1
Liver transplant with post-operative liver disorder NOS[a]	1
Multi-organ failure	1
Primary sclerosis cholangitis	1
Progressive liver failure	7
Prothrombin time elevation	3
Total	**227**

a - NOS = not otherwise specified

(Source: Applicant's Amendment 0012, April 6, 2009 document, p. 26)

2.3.4 Hepatic Summary Findings:

- Majority of cases involved Subutex (127 patients or 55.9%); Suboxone 76 patients or 33.4%; Other Buprenorphine products (24 patients or 10.6%)
- Fifty six (56) percent of cases of hepatic adverse events (126/227) involved patients who had cofactors for Hepatoxicity such as viral hepatitis, HIV, IVDU of Subutex or ethanol abuse
- Many cases were complicated by use of concomitant medications which may have been either the primary etiology for the hepatic dysfunction or exacerbated liver effects of buprenorphine

2.3.4.1 *Reviewer Comments:*

The overall conclusion in the review by Dr. James Kaiser (OSE) dated 5/15/09 was that buprenorphine may aggravate hepatic dysfunction, but the data do not strongly support an etiologic role. This reviewer is in agreement. Some reported cases involve patients using various formulations of buprenorphine for pain, which is not currently reflected in the wording of the label. In addition, the existence of cases with positive de-challenge is not mentioned in current labeling. Finally, fatal cases have been reported in which a role of buprenorphine cannot be ruled out. It is recommended that the proposed label reflect the following changes:

3 Buprenorphine Use in Pregnancy

3.1 Use in Pregnancy

A Review of the Applicant's internal data and selected literature references was performed by this reviewer regarding the use of buprenorphine in pregnancy.

The current Suboxone strip proposed label is as follows:

Pregnancy

(b) (4)

The above proposed label contains language that " (b) (4) is not compliant with Agency regulatory requirements.

Regulatory requirements for Pregnancy Category C are as follows: Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The labeling shall contain a description of the animal studies.

(b) (4)

Table 9 below summarizes the Applicant's internal postmarketing data regarding buprenorphine AEs and SAEs during pregnancy. These cases are categorized by specific drug name (Subutex, Suboxone, other buprenorphine).

Table 9: Post Marketing Buprenorphine AEs and SAEs during Pregnancy

	All Buprenorphine (1/1/1997 – 10/31/08)	**Subutex SL (1/1/1997 – 10/31/08)**	**Suboxone SL (1/1/03 – 10/31/08)**	**Buprenorphine (Other) 1/1/05 – 10/31/08**
AEs (CR=Case Reports)				
Total AEs	3,052 (1268 CR)	1,182 (656 CR)	1,799 (590 CR)	71 (22 CR)
Exposure during pregnancy	1445	633	791	21
Pregnancy	104	35	69	*
Spontaneous abortions	83	24	57	*
SAEs (CR= Case Reports)				
Total SAEs	604 (198 CR)	247 (113 CR)	320 (76 CR)	37 (9 CR)
Exposure during pregnancy	216	104	104	8
Spontaneous abortions	80	21	57	*
Induced abortions	33	*	*	*

* Denotes information not available in the Applicant's submission
(Source: Table prepared by reviewer from data provided in Applicant's Submission)

In addition to the pregnancy exposure summarized in Table , the findings for pregnancy exposure from 5/1/08 to 10/31/08 (taken from the Applicant's 4 month Safety Update) were as follows:

- Subutex SL – A total of 136 events of drug exposure during pregnancy was reported. Of those, there were 19 serious case reports. These reports included three case of intrauterine death (Case # PW/020702/351; RB-2408-2008; RB-2748-2008), 7 cases of spontaneous abortion and three case of premature labor or premature infant.
- Suboxone – A total of 720 adverse events were reported which included 257 events of drug exposure during pregnancy. There were 24 serious case reports (12 updated reports). The SAEs included 11 reports of spontaneous abortion, two cases of premature labor or birth and seven cases in which abortion was induced (including selective abortions).
- Buprenorphine (other) – A total of 20 AEs were reported which included 13 events of drug exposure during pregnancy. There were seven case reports concerning SAEs. These SAEs included an intrauterine death (Case # RB-1929-2008), a case of fetal bradycardia, two reports of spontaneous abortion, a caesarean section with hemorrhage, myomectomy, hemorrhagic shock with a live birth, one premature birth and a case of pyelonephritis.

The literature review for Buprenorphine use in pregnancy is found in Section 3.3 of this review under Literature review (Use in Pregnancy and Lactation Including Neonatal Withdrawal Effects.

3.2 Neonatal (in utero) Exposure and Neonatal Withdrawal (Abstinence) Syndrome

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. According to the Applicant (from information based on postmarketing reports) the time to onset of neonatal withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been reports of convulsions and in one case apnea and bradycardia were also reported.

Current proposed label for Suboxone strip as follows:

3.2.1 Post-Marketing Experience

The table below displays the Applicant's postmarketing data regarding neonatal (in utero) exposure and neonatal withdrawal syndrome categorized by specific drug name (Subutex, Suboxone, other buprenorphine).

Table 10 : Post Marketing Buprenorphine Neonatal (In utero) Exposure and Neonatal Drug Withdrawal Syndrome

	All Buprenorphine (1/1/1997 – 10/31/08)	**Subutex SL (1/1/1997 – 10/31/08)**	**Suboxone SL (1/1/03 – 10/31/08)**	**Buprenorphine (Other) 1/1/05 – 10/31/08**
AEs (CR=Case Reports)				
Total AEs	877 (354 CR)	618 (256 CR)	177 (36 CR)	58 (43 CR)
Drug Withdrawal syndrome (neonatal)	212	131	29	34
Drug Exposure During Pregnancy	140	83	52	*
Drug Withdrawal Syndrome	*	56	*	*
SAEs (CR=Case Reports)				
Total SAEs	774 (303 CR)	563 (224 CR)	144 (31 CR)	56 (41 CR)
Drug Withdrawal syndrome (neonatal)	188	120	29	34
Drug Exposure During Pregnancy	122	73	44	*
Drug Withdrawal Syndrome	*	54	*	*

* Denotes information not available in the Submission
(Source: Table prepared by reviewer from data provided in the Applicant's Submission)

In addition to the in utero and neonatal exposure summarized in Table , the findings for in utero and neonatal exposure from 5/1/08 to 10/31/08 (taken from the Applicant's 4 month Safety Update) were as follows:

- Subutex SL – A total of 24 serious cases which related to neonates was reported. The most frequently reported SAE was 19 cases of neonatal withdrawal syndrome. (More than one SAE occurred in some cases). Four cases included neonatal respiratory distress syndrome or respiratory distress, three cases of premature baby, two cases of exomphalos. One case included exposure in breast milk.
- Suboxone – A total of 78 AEs were reported from 14 case reports. Eight serious cases (more than one SAE occurred in all cases) were reported with neonatal withdrawal syndrome or withdrawal syndrome in 7 cases. Other events reported included one case of irritability and jaundice, one case of fetal growth retardation and small for dates baby, and two cases of exposure in breast milk.
- Buprenorphine (other) – A total of 47 adverse events reported from 38 case reports. There were 35 case reports (CR) concerning 41 SAEs. Neonatal withdrawal syndrome was reported in 32 of the cases. There was one case that experienced SAEs of drug dependence, premature baby, Fallot's tetralogy, periventricular leukomalacia and death. One case experienced brain injury, cerebrovascular disorder, and drug exposure during pregnancy.

Reviewer Comment: The review of the postmarketing data submitted by the Applicant supports the proposed buprenorphine label and warning that buprenorphine and naloxone soluble film should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

3.3 Literature review (Use in Pregnancy and Lactation Including Neonatal Withdrawal Effects):

The Applicant cited 19 literature references pertaining to use in pregnancy and lactation (including neonatal withdrawal effects) in the initial NDA 22-410 submission with an additional 4 references in the 4 month safety update. The relevant cited articles were read and summarized by this reviewer. Articles which the Applicant cited to support a label claim, those which were randomized, controlled studies or those which supported the current proposed label or provided new information are discussed in more detail as follows:

(Study 1) Reference/Title: Jones, HE, Johnson Re, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depen 2005;79:1-10

Design: Randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial designed to compare NAS in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women

Primary Outcome Measures:

- Number of neonates requiring morphine drops for NAS
- Peak NAS score
- Total amount of morphine drops administered to treat NAS and
- Total days of neonatal hospital stay from delivery until discharge from the hospital

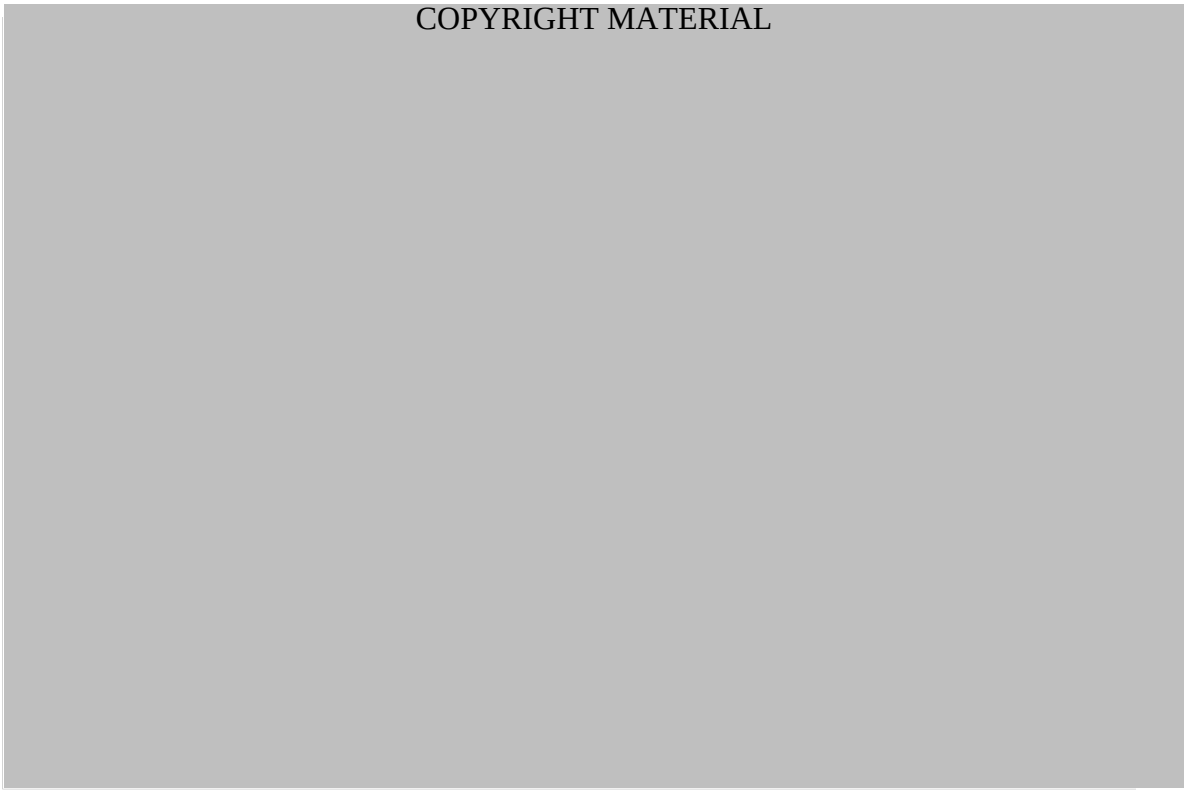
Secondary outcome measures: birth and maternal treatment

Methods: Subjects received daily administration of either SL buprenorphine or oral methadone using flexible dosing of 4-24 mg or 20-100 mg respectively.
Of the 30 randomized patients, 20 delivered while enrolled in the study and 10 dropped out during the study. One buprenorphine-maintained mother delivered twins (therefore data for variables known to be altered by twin status were not included in the statistical analysis). The final sample size enrolled in treatment at delivery was 11 women stabilized on methadone and 9 women stabilized on buprenorphine.

Results: Twenty (20%) of buprenorphine-exposed and 45.5% of methadone-exposed neonates were treated for NAS. The total amount of medication administered to treat NAS in methadone-exposed neonates was 3X greater than for buprenorphine-exposed neonates. Buprenorphine exposed neonates remained in the hospital for a shorter period of time (1.3 days difference) than methadone exposed. One buprenorphine-exposed neonate (20%) and two methadone-exposed neonates (46%) were admitted to the NICU and spent 2, 4 and 7 days, respectively. None of the NICU admissions was due to opioid withdrawal. The buprenorphine-exposed neonate NICU admission was due to streptococcal septicemia. One of the methadone-exposed neonate NICU admissions was due to a high bilirubin level and the other due to respiratory distress. Daily peak NAS total scores over all observation days did not significantly differ between groups.

The Table 11 below presents a summary of the data regarding the secondary outcome measure of birth and maternal treatment outcomes. There was no significant difference in the measures of birth weight, gestational age and Apgar scores at delivery and no major or minor congenital abnormalities were observed in either group.

Table 11: Buprenorphine versus methadone exposed neonatal and maternal outcomes



(Source:Jones, HE, et al , Drug Alcohol Depen 2005;79:1-10, p. 8)

Study Limitations: Small sample size limits the power associated with the tests of significance. Women were not enrolled in the study until gestational week 16 to minimize any possible physical teratogenic effects. Therefore, the extent to which these findings generalize to neonates conceived during methadone or buprenorphine maintenance is unknown.

(Study 2) Reference /Title: Fischer G, Ortner R, et al, Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction 2006; 101:275-281.

Design: Randomized, double-dummy, double-blind, flexible dosing comparison study

Methods: 18 women randomized (9 methadone or 9 buprenorphine). After drop outs, data was available from 14 cases (six in methadone and eight in buprenorphine) who received sublingual buprenorphine tablets (8-24 mg/day) or oral methadone solution (40-100 mg/day) with matched placebos.

Findings: There was a somewhat greater retention in the buprenorphine group but significantly lowered use of additional opioids in the methadone group. There was earlier onset of NAS in neonates born to the methadone (mean 60 hours) than to the buprenorphine groups (mean 72 hours) after last medication. Fifty seven percent (57%) required NAS-treatment.

Of the 14 neonates, six (three from mothers in each treatment group) experienced no more than mild NAS and did not require treatment. For the 8 neonates who required treatment for their NAS symptoms, neonates of methadone-maintained mothers required treatment on average 12 hours earlier than those born to the buprenorphine maintained group. The mean duration of treatment for NAS was 5.3 and 4.8 days in the methadone and buprenorphine groups, respectively. There was no difference in the mean cumulative dose of morphine required to manage NAS in the two groups.

Limitations: Small sample size with limited power to detect differences

(Study 3) Reference/Title: **Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S; Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenorphine substitution. Drug Alcohol Depend 2006;82(3):250-7. Epub 2005 Oct 27.**

Design: Prospective multi center observational study

Methods: All neonates whose mothers has been maintained during pregnancy on methadone or buprenorphine were included by 34 French perinatal centers with specialized staff for care of these pregnant drug abusers

Findings. Two hundred and forty-six pregnant women were included: 93 (38%) methadone and 153 (62% buprenorphine). Social and perinatal data, prenatal care and factors correlated with poor prenatal care were reported. Forty-six percent of the pregnant women had good prenatal care; 88% had peridural analgesia; mean birthweight was 2822g; mean gestational age was 38.6 weeks; prematurity 12.3% (<37 weeks); intra-uterine growth retardation was 32%. Sixty-five percent neonates had withdrawal neonatal syndrome beginning at a mean age of 40 hours. Half of them were treated, mainly with morphine hydrochloride. No baby died. Methadone group experienced 38% intra-uterine growth retardation and high dose buprenorphine group experienced 31%.

Conclusion: There were no major differences between the two study groups in terms of perinatal outcome. There was slightly delayed onset of NAS for the methadone group (mean age at maximum score was 80 hours for methadone vs. 66 hours for buprenorphine).

(Study 4) Reference/Title: Johnson RE, Jones HE and Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 2003;70:S87-S101.

Methods: Review of 21 published reports representing approximately 15 evaluable cohorts of infants exposed to buprenorphine in utero from 1995 to 2002

Findings: Of approximately 309 neonates exposed, a neonatal abstinence syndrome (NAS) was been reported in 62% of neonates with 48% requiring treatment. Greater than 40% of these cases are confounded by illicit drug use. The NAS associated with buprenorphine was reported to generally appear within 12-48 hours, peak at approximately 72 to 96 hours, and lasts for 120-168 hours. These results appear similar to or less than that observed following *in utero* exposure to methadone.

(Study 5) Reference/Title: Kahila H, Saisto T, Kivitie-Kallio S, Haukkamaa M, Halmesmaeki E. A prospective study on buprenorphine use during pregnancy: Effects on maternal and neonatal outcome. Acta Obstet Gynecol Scand 2007a;86(2):185-190.

Design: Prospective design

Methods: Over the three-year period from 2002 to 2005, 67 pregnancies of 66 buprenorphine users were monitored. The pregnancies and deliveries were uneventful.

Findings: No increased incidences of premature birth, C-section, low Apgar scores (≤ 6) or umbilical artery ph <7.5 at birth when compared to national register, despite the lower birth weight. However, a total of 91% of infants needed treatment in a neonatal care unit, 76% had NAS and 57% needed morphine replacement therapy. Two sudden infant deaths occurred later (3%) with dates not listed.

(Study 6) Reference/Title: Colombini N, Elias R, et al; Hospital morphine preparation for abstinence syndrome in newborns exposed to buprenorphine or methadone. Pharm World Sci 2008; 30:227-234

Methods: Studied the use of oral morphine solution to treat NAS was assessed in neonates exposed to either methadone (n=9) or buprenorphine (n=13) in utero

Findings: All pregnancies were normal with no abnormal birth outcomes. Onset of NAS was within 24 hours after birth in methadone-exposed neonates and generally within 48 hours in buprenorphine-exposed neonates but could be delayed up to 7 days.

Methadone group required higher doses of morphine solution than buprenorphine during the first 38 days of treatment.

The mean duration of morphine treatment was longer in the methadone group compared with the buprenorphine group (45 vs 28 days).

NAS was less severe in neonates exposed to buprenorphine than to methadone, unless the mothers were abusing other psychotropic medications or illicit opioids

(Study 7) Reference/Title: Hytinantti T, Kahila H, et al. Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero. Acta Paediatrica 2008; 97:1040-1044

Methods: Reported on 58 neonates exposed to buprenorphine in utero. IV buprenorphine was used in 27 (47%) of the pregnancies after 36 weeks of gestation. In five (9%) cases the route of buprenorphine administration was unknown. 38 of 58 neonates required morphine treatment for NAS.

Findings: Of the 58 Neonates exposed, three (5%) premature births were reported. One of the premature births had tetralogy of Fallot and severe periventricular leukomalacia. The mother was reported noncompliant with prenatal care and had poorly controlled Type I diabetes. Two other neonates had developmental anomalies (one had VSD, microtia and inguinal hernia and the other retention of testis). Two neonates required a blood transfusion (one due to ABO immunization and the other due to Rhesus (Rh) immunization. Ten neonates had EEGs with findings noted as abnormal (not specified) for 2 of the 10.

The mean duration of morphine treatment and hospitalization were 20±10 days and 25 ± 19 days respectively. Mean birth weight and head circumference of the neonates exposed to buprenorphine in utero were below average (-0.7 and -0.5 standard deviations respectively).

Neonates from mothers reporting IV buprenorphine use had a mean Finnegan score on Day 1 of 6.8±2.7 compared with 4.7±2.1 for neonates from mothers reporting SL buprenorphine use (p=0.002).

(Study 8) Reference/Title: Kakko J, Heilig M, et al. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug and Alcohol Dependence 2008; 165(3):400-401 (2008) (Sweden)

Design: Population based comparison of consecutive, prospectively followed buprenorphine-exposed pregnancies

Methods: Participants included all 47 pregnancies in 39 women with opiate dependence and buprenorphine maintenance treatment 2001-2006, and all 35 methadone-exposed pregnancies (26 women) 1982-2006

Findings: Buprenorphine maintenance treatment did not appear to lead to growth restriction and had a lower rate of NAS in 47 uneventful live birth (2 twin pair), one stillbirth at 38 weeks) and 1 miscarriage at 18 weeks. There were 35 neonates born after exposure to methadone, two of whom died of sudden infant death syndrome (SIDs). NAS occurred in 19 (40.4%) buprenorphine-exposed neonates compared with 77.8% of methadone-exposed neonates with most cases mild in the buprenorphine group. When buprenorphine treatment began prior to conception, NAS at any level was less frequent than in neonates with treatment initiated post-conception .

The following articles in Table 12 were referenced by the Applicant in the submission. They represent case reports and uncontrolled studies and are summarized as follows:

Table 12: Additional Cited Articles Use of Buprenorphine in Pregnancy and Neonatal Withdrawal Syndrome

Article/ Summary	Findings
Loustaneau (2002) (France) Reviewed 102 case reports of newborns exposed in utero to buprenorphine between 1996 and 2000	Infants delivered at term; no significant birth weight changes compared to neonates not exposed to buprenorphine
Jones (2005) (a) Safety and withdrawal discomfort associated with transitioning from short acting morphine to double-blind SL buprenorphine (n=8) or oral methadone (n=10) was evaluated in pregnant opioid dependent women who were part of a larger, randomized controlled study (Jones, 2005 (b) comparing NAS in mothers treated with SL buprenorphine or with oral methadone.	No significant differences between the groups
Jones (2006) Four pregnant inpatients who had participated in Jones 2005 (b) study were switched from methadone to five days of immediate release morphine then to buprenorphine.	Withdrawal symptoms appeared during buprenorphine induction and none of the women continued on buprenorphine maintenance All neonates were born well and had outcomes typical for this population
Ebner (2007) Evaluated 53 neonates born to mothers maintained on methadone (22), morphine (17) or buprenorphine (14)	All groups had similar Apgars with no difference in weight, length, or head circumference. Treatment for NAS was required by 68% neonates in the methadone group, 82% in the morphine group and 21% in the buprenorphine group. The mean duration from birth to the requirement of treatment was 33 hours for morphine; 34 hours for buprenorphine and 58 hours for the methadone maintained.
Lacroix (2004) (France) Followed 34 pregnant women exposed to buprenorphine maintenance for opiate dependence	The buprenorphine exposed pregnancies resulted in 31 live births, one stillbirth, one spontaneous abortion and one voluntary termination. NAS was observed in 13 cases (41.9%) and eight of those babies required opiate treatment. Two neonates had a malformation (a premature ductus arteriosus structure and a tragus appendix)
Kayemba-Kay; Laclyde (2003)	Thirteen infants were born (8 male and 5 female)

(France) Retrospective case records of infants admitted to the NICU and/or special care baby unit (SBU) from January 1994- December 2000 for surveillance and/or treatment of buprenorphine	with normal Apgar scores. Four infants were small for gestational age, none was dysmorphologic and none was treated for fetal distress. NAS occurred in 11 cases (85%) and required treatment in 10 cases. 7 children had hypertonia, jerky movements or jitteriness that resolved over 9 months.
Schindler (2003) Pilot study of 2 patients who received buprenorphine (6 or 12 mg/day) at conception and throughout pregnancy followed to term	Both cases delivered healthy babies with normal birth outcomes. Neither baby required NAS treatment. The patient receiving 12 mg/day breast fed for 6 months and the neonate had no complications.
Strengell (2005) (Finland) 9 patients who received buprenorphine during pregnancy (including 2 who received treatment throughout pregnancy)	One patient had induced abortion due to fetal abnormalities (hypoplasia of right cardiac ventricle, left ventricular dilation, early closure of arterial duct, and pulmonary hypertension)
Ross (2004)	Single case of pregnant woman taking buprenorphine for heroin dependence. The fetus was small for gestational age. The baby did not show full signs of withdrawal but had signs of "irritability"

(Source: Table prepared by reviewer from data provided by Applicant's Study Report)

Discussion: The findings of the studies of neonatal outcomes in patients using buprenorphine during pregnancy are equivacol and do not support a benefit of buprenorphine over methadone use especially in cases where patients continue to use illicit drugs

Reviewer Comments:
Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy and is reflected in the current proposed label for Suboxone soluble film (NDA 22-410). The information submitted in the Applicant's postmarketing data and a review of the literature does not support recommending use of buprenorphine in pregnancy at this time.

Some terms not currently captured in the labeling have been reported in infants exposed in utero to buprenorphine. The labeling should be revised to read:

(b) (4)

Buprenorphine and Nursing Mothers:

(b) (4)

Two studies (Grimm and Johnson) were reviewed which dealt with concentrations of buprenorphine and norburprenorphine in human breast milk. The conclusions from both of those studies are that drug exposure to the infant is considered to be low.

Reviewer's Comment: The current label adequately reflects use of Suboxone in nursing mothers. No new safety information regarding this population was identified in this review.

4 Accidental (Unintentional) Pediatric Exposure

One of the objectives articulated by Reckitt Benckiser for the development of the Suboxone (b) (4) was the provision of a unit-of-use packaging that would deter accidental pediatric exposure.

Applicant's proposed label:

(b) (4)

In the Applicant's Summary of Clinical Safety, a summary of information about the extent and consequences of accidental pediatric exposure to buprenorphine was provided. It is reported that, to date, no deaths have occurred due to unintentional pediatric exposure to Suboxone or Subutex, which have been reported in the literature or in unpublished data available to the Applicant.

4.1 Poison Control Center Data

Reckitt Benckiser has contracted with the (b) (4) to provide specific information about pediatric exposures to buprenorphine products. The table below was constructed by the review team using Unpublished (Internal Reckitt Benckiser) Data combined with distribution data provided by OSE to show the number of reports of accidental exposure per million prescriptions dispensed.

Table 13: (b) (4) Toxic Exposure Surveillance System Annual Reports All Buprenorphine

Age	Year	Number Cases	Prescriptions Dispensed[1]	Comments
All aged children	2004	59	(b) (4)	
< 6 yo	2006	192		
< 6 yo	2007	412		
< 6 yo	2008[2]	589		

(b) (4) data from OSE review
[2]Reports from Q1-3 only; sales from Q1-4

In order to place this data into some context in comparison to accidental pediatric exposures to other opioids, the review team constructed the table below. In the this table, the number of mentions of specific drugs in cases involving patients under age 6 was

taken from the 2007 report of the (b) (4) . The number of poison control center mentions in patients under 6 for buprenorphine products was taken from Reckitt Benckiser's 7/3/08 report of their post-marketing surveillance program for Suboxone and Subutex. In order to place the number of reports into context of the extent of distribution of the various products, distribution data from a consult prepared recently by the Drug Use Data Analysis team in OSE for the Division of Oncology. This consult included a tabulation of distribution data for various opioids; distribution for 2007 was extracted from this tabulation and used to create a denominator for comparing numbers of reports to numbers of prescriptions. This is one of many imperfect ways of attempting to correct numbers of reports for extent of distribution, but it does allow some sense of context and illustrates that the number of accidental exposures of small children to buprenorphine is very high, considering the extent of distribution as can be seen in Table 14.

Table 14. Poison Control Center Reports in Children Under Age 6, 2007

Substance	PCC reports	Million Rxs	Reports per Million Rx
Buprenorphine (all)	419	(b) (4)	
Subutex	13		
Suboxone	399		
Codeine	280		
Meperidine	43		
Methadone	318		
Morphine	264		
Oxycodone	525		
Pentazocine	8		
Propoxyphene	27		
Tramadol	709		

[1]Note that methadone dispensed via opioid treatment programs is not included in this total; therefore distribution is underestimated and the reporting rate is overestimated.

4.2 Literature Review

A review of the Applicant's submitted analysis of literature references was performed. In an email from the Applicant to the Agency, they referenced articles by Bailey J., Geib, AJ, Hayes BD, Spadari; and Yassen A. These articles were reviewed in full by this reviewer. However, the article by Spadari could not be located using a literature search. An information request was sent to the Applicant requesting a copy of that reference. At the time of this review, the copy has not yet been received.

Summaries of the referenced literature as follows:

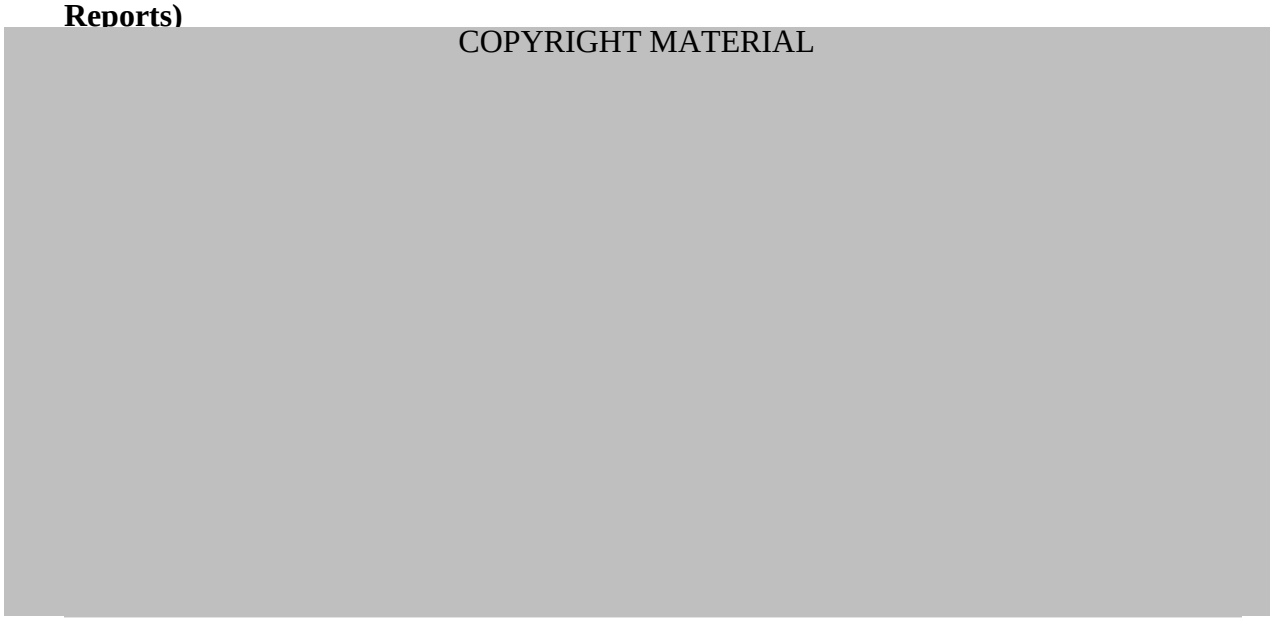
(Study 1): Reference/Title: Geib AJ, Babu K, Ewald MB, Boyer EW. Adverse effects in children after unintentional buprenorphine exposure. Pediatrics 2006;118:1746-1751.

Design: Cases series report of five children aged 15 to 22 months who experienced buprenorphine toxicity due to unintentional exposure and required either naloxone therapy or mechanical ventilation

Methods: Review of cases for identifying clinical presentation, treatment interventions and outcomes.

Table 15 below describes parameters of interest as stated above.

Table 15: Clinical Presentation of Buprenorphine Toxicity in Children (Case Reports)



(Source: Geib AJ , et al Pediatrics 2006;118: p. 1746)

Findings: The authors of this article conclude that pediatric buprenorphine exposure produces the same syndrome of apnea, mental-status depression and miosis as is seen in opioid toxicity.

They further describe the behaviors of toddlers which places them at such great risk:

- Children may be inclined to suck on or chew tablets which may lead to buccal absorption of the drug. Despite the poor bioavailability of buprenorphine, children who suck on a tablet may receive a toxic dose
- Opioid-naïve children would be expected to have a greater μ receptor sensitivity

- Placing the medication in the mouth may result in more absorption than swallowing the tablet
- Buprenorphine may have an exaggerated effect on respiratory drive in children

The conclusions and recommendations of the authors of this article are as follows:

- Pediatric experience with naloxone suggest that doses of naloxone in excess of the recommended 0.1 mg/kg may be required
- The reversal of buprenorphine-induced respiratory depression by naloxone may be delayed relative to other opioids
- All children in this case series had reversal of respiratory depression within minutes of receiving naloxone
- Recurrent respiratory depression after naloxone may require a continuous infusion of naloxone
- Toddlers with definite or suspected buprenorphine exposure should have extended observation given buprenorphine prolonged duration of action

(Study 2) Reference/Title: Bailey, JE, Campagna E, et al. The Underrecognized Toll of Prescription Opioid Abuse on Young Children" Annals of Emergency Medicine. Vol. 53, No. 4: April, 2009.

Design: Prescription opioid exposures in children was examined in the United States using the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System specifically searching for opioid exposures involving children younger than 6 years from first quarter 2003 through second quarter 2006.

Findings: A total of 9,179 children were exposed to a prescription opioid. Nearly all exposures involved ingestion (99%) and occurred in the home (92%). The article used the following standard definitions[3] as given in the American Association of Poison Control Centers. Instructions for the American Association of Poison Control Centers Toxic Exposure Surveillance System (2001).

- Minor effect: The patient exhibited some symptoms as a result of the exposure, but they were minimal bothersome to the patient
- Moderate effect: The patient exhibited symptoms as a result of the exposure, which are more pronounced, more prolonged or more of a system nature than minor symptoms. Usually, some form of treatment is or would have been indicted. Symptoms were not life threatening
- Major effect: The patient has exhibited symptoms as a result of the exposure, which were life-threatening or resulted in significant residual disability or disfigurement
- Death: The patient died as a result of the exposure or as a direct complication of the exposure when the complication was unlikely to have occurred had the toxic exposure not preceded the complication

[3] American Association of Poison Control Centers. Instructions for the American Association of Poison Control Centers Toxic Exposure Surveillance System (2001). Available at: http://www.aapcc.org/MEMBERS/tess%20manual%202002/fielddefs/outcome2002.pdf

Compared to other drugs which were evaluated in the study (for which 62-78% of mentions had no effect) only 32% of buprenorphine cases had an outcome of no effect. Therefore, buprenorphine was examined in more detail because of a higher proportion of mentions associated with an effect. Nine (9) Subutex and 136 Suboxone (buprenorphine and naloxone combination) mentions were reported during the study period, most likely explained by the fact that most patients who were prescribed buprenorphine in 2006 received Suboxone.

Exposures and associated medical outcomes were characterized with an opioid mention as the unit of analysis. Each mention represented a prescription opioid that a child was exposed to and for which information was gathered through a call to a participating poison center. The authors of the article noted that a case may include multiple mentions if the exposed individual was exposed to more than 1 prescription opioid of interest.

Table 16 provides details regarding the characteristics and outcomes of childhood exposures.

Table 16: Characteristics and outcomes of childhood (< 6 years of age) exposures by opioid analgesic

(Source: The Underrecognized Toll of Prescription Opioid Abuse on Young Children" (Vol. 53, No. 4: April, 2009, Annals of Emergency Medicine),Bailey et al, p 421

The authors of the article made the following conclusions regarding accidental pediatric exposure to buprenorphine:

- Buprenorphine exposures were associated with no deaths, 5 major effects and 25 moderate effects
- An outcome of no effect or minor effect was reported in 57% of Subutex and 78% of Suboxone
- For those mentions with a known outcome, 29% of Subutex mentions and 2% of Suboxone mentions were associated with a major effect
- Administration of naloxone after ingestion of buprenorphine resulted in a beneficial response

Limitations: Not all exposures were captured because not all poison centers participate in the RADARS System. There are also inherent limitations of passive data collection and reliance on verbal reports.

(Study 3) Reference/Title: Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. Pediatrics 2008; 121:e782-e786: Toxicity of Buprenorphine Overdoses in Children

Design: A retrospective review of buprenorphine overdoses in children <6 years of age

Objectives: To analyze buprenorphine overdoses in young children reported by US poison centers to the Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS)

Methods: A retrospective review of buprenorphine overdoses in children < 6 yo reported to the RADARS from November 2002 through December 2005, Patients lost to follow up and those ingesting multiple substances were excluded

Findings: Eighty-six cases met inclusion criteria. In the 54 children who developed toxicity, the clinical effects included drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities. The mean time to onset of effects was 64.2 minutes, with a range of 20 minutes to 3 hours. Duration of clinical effects was under 2 hours in 11%, 2 to 8 hours in 59%, 8 to 24 hours in 26%, and >24 hours in 4%. Children who ingested ≥2 mg of buprenorphine were more likely to experience clinical effects and all of the children who ingested >4 mg experienced some effect. No child ingesting <4 mg experienced a severe effect. Of the 22 children administered naloxone, 67% had at least a partial response.

The authors concluded that buprenorphine overdoses are generally well tolerated in children but significant central nervous system (CNS) and respiratory depression can occur. Any child < 2 yo with more than a lick or taste should be referred to the emergency department for a minimum of 6 hours of observation. Naloxone can be used to reverse respiratory depression.

(Study 4) Reference/Title: Yassen, A, et al, Pharmacokinetic-Pharmacodynamic Modeling of the Effectiveness and Safety of Buprenorphine and Fentanyl in Rats, Pharmaceutical Research, Vol 25, No. 1, Jan 2008, p 183-193

Findings: The safety index for buprenorphine was 13.54 (compared to fentanyl of 1.20).

The following abstracts, case reports or case series were also discussed by the Applicant and are summarized below in Table 17.

Table 17: Published Abstracts (Case Reports and Case Series)

Age	Drug/Dosage	# Cases (Exposure)	Outcome	Source
22 months – 5 yo	All Buprenorphine	3	Symptomatic (but none required intensive care)	Blanc et al, 2004
4 yo	Subutex (4mg)	1	Mild case; bilateral miosis only symptom	Gaulier et al, 2004
2 yo	Ingested 1 Suboxone 8 mg/2 mg tablet	1	Somnolent; decreased RR, miosis. Improved with Naloxone IV. Discharged home without sequalae after 24 hour observation	Truitt et al (2008)
2 yo	Ingested 1 Suboxone 8 mg/2 mg tablet	1	Required naloxone drip x 44 hours; discontinued 96 hours post-ingestion. Required intubation for 7 hours. Reported as postmarketing surveillance (Case 3 RB-6439-2008)	McKeown et al (2008)
Information not reported	All buprenorphine	58 (case series Pittsburg, PA	No deaths	Kurta et al (2008)
Information not reported	All buprenorphine	0 in 2003 25 in 2007	Increase in the number of reports of buprenorphine from 0 in 2003 to 25 in 2007 in Boston, MA	Longfellow (2008)

(Source: Table prepared by reviewer from data provided in Applicant's Submission)

4.3 Reviewer Comments (Accidental Overdose (Exposure) in Children):

- *Number of pediatric accidental exposure cases has increased from 192 in 2006 to 589 in 2008, commensurate with increase in distribution.*
- *Majority < 6 yo and in that population, those < 3 yo appear more frequently affected.*
- *In data where comparison to methadone was available, methadone cases appeared to have more severe outcome than buprenorphine.*
- *The most common adverse events reported were somnolence, emesis, and miosis*
- *Treatment included naloxone, Iv fluids, activated charcoal, oxygen and ipecac.*
- *Most patients had minor or moderate adverse events reported*
- *More severe cases required repeated naloxone and respiratory support in some cases*

5 Labeling Changes Recommended

5.4 (text in PLR format) Hepatitis, Hepatic Events

(b) (4)

APPENDIX 1. Subjects with abnormal liver function test results at baseline or follow-up (Study RB –US-0002)

Subject ID	Analyte	Results (baseline / discharge) U/L	Outcome
Group A			
105	Alk. Phos.	118* / 133*	↑
108	ALT	38 / 72*	↑
113	AST	33 / 36*	↑
116	ALT AST	25 / 84* 19 / 45*	↑ ↑
122	AST Alk. Phos.	34* / 35* (30 with f/u) 116* / 115	↑ Improved
136	ALT AST	53 / 62* 47* / 52*	↑ ↑
139	ALT	10 / 41*	↑
147	Alk. Phos.	80 / 136*	↑
168	ALT AST	62* / 160* 50* / 119*	↑ ↑
179	ALT AST	21 / 107* 19 / 45*	↑ ↑
Group B			
101	ALT AST	160* / 226 (211 with f/u) 71* / 84* (105 with f/u)	↑ ↑
102	ALT	23 / 62*	↑
106	ALT AST	73* / 25 65* / 19	Improved Improved
128	ALT AST Alk. Phos.	20 / 167* 19 / 128* 84 / 127*	↑ ↑ ↑
140	AST	39* / 23	Improved
145	ALT AST	40 / 73* 61* / 72*	↑ ↑
165	ALT AST	83* / 81* 65* / 47*	Improved Improved
Untreated			
117	Alk. Phos.	124* / 141*	↑
120	ALT AST	108* / 83* 69* / 45*	Improved Improved
142	ALT AST	87* / 135* 57* / 83*	↑ ↑
153	ALT AST	27 / 67* 29 / 52*	↑ ↑
164	AST	47* / 40*	Improved

(Source: Table prepared by reviewer from Applicant's submitted data)
***Analyte result above the normal laboratory reference Limit.** (↑ = increased)

Laboratory reference limits: ALT 9-60 U/L males, 6-40 U/L females;
AST 10-40 U/L males 20-49 y/o, 10-35 U/L males ≥50 y/o, 10-30 U/L females 20-44 y/o, 10-35 U/L females ≥45 y/o ; Alk Phos. 40-115 U/L.

6 REFERENCES CITED IN REVIEW

Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. J Subst Abuse Treat
2004; 27:75 -82

Bailey, JE, Campagna E, Dart RC. The RADARS System Poison Center Investigators. The under recognized toll of prescription opioid abuse on young children. Ann Emerg Med 2008 Sep 5.

Berson A, Gervais a, Cazals D, Boyer N, Durand F, Bernuau, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. J. Hepatol 2001;34:346-350

Blanc B, MacBullen G, Maestracci M, Zebiche H, Rodiere M. Accidental intoxication with opiates agonists: the experience of the U.A.U.P. in Montpellier in 2003. General Paediatrics 2004; 11:739-772.

Bruce RD, Altice FL. Case series on the safe use of buprenorphine/naloxone individuals with acute hepatitis C infection and abnormal hepatic liver transaminases. Am J Drug Alcohol Abuse 2007;33:869-874

Colombini N, Elias R, Busuttil M, Dubuc M, Einaudi M-A, Bues-Charbit M. Hospital morphine preparation for abstinence syndrome in newborns exposed to buprenorphine or methadone. Pharm World Sci 2008;30:227-234.

Dugarin, J. et al. Opiate substitution. Concours Medical 2005; 127(37):2113-2114.

Ebner N, Rohrmeister K, Winklbaur B, et al. Management of neonatal abstinence syndrome in neonates born to opioid-maintained women. Drug Alcohol Dependence 2007;87-131-138.

Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, Aschauer H. Methadone versus bupernorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction 2006;101:275-281.

Gaulier JM, Charvier F, Monceaux F, Marquet P, Lachatre G. Ingestion of high-dose buprenorphine by a 4-year-old child. J toxicol 2004;42(7):993-995.

Geib AJ, Babu K, Ewald MB, Boyer EW. Adverse effects in children after unintentional buprenorphine exposure. Pediatrics 2006; 118:1746-1751.

Grimm D, Pauly E, Pőschl J, Linderkamp O, Skopp G. Bupernorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit 2005;27(4):526-530.

Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. Pediatrics 2008; 121:e782-e786: Toxicity of Buprenorphine Overdoses in Children

Herve, S, Riachi G, Noblet C, et al. Acute hepatitis due to buprenorphine administration. Eur J Gastroenterol Hepatol 2004;16(10):1033-1037.

Houdret N, Asnar V, Szostak-Talbodec N, Leteurtre E, Humbert L, Lecomte-Houcke M, et al. Severe hepatonephritis and buprenorphine intoxication. Acts Clinica Belgica 1999;51(1):29-31.

Hytinantti T, Kahila H, Renlund M, Järvenpää A-L, Halmesmäki E, Kivitic-Kallio S. Neonatal outcome of 58 infants exposed to maternal buprenorphine *in utero.* Acta Paediatrica 2008;97:1040-1044.

Johnson RE, Jones HE, Jasinski, DR, et al. Buprenorphine treatment of pregnant opioid dependent women: Maternal and neonatal outcomes. Drug Alcohol Depend 2001;63:97-103.

Johnson RE, Jones HE and Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 2003; 70:587-S101.

Jones HE, Johnson RE, Jasinski DR, Milio L. Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone. Drug Alcohol Depend 2005;78:33-38.

Jones HE, Johnson RE, Jasinski DR, O'Grady KE, Chisholm CA, Choo RE, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depend 2005; 79:1-10.

Jones HE, Suess P, Jasinski DR, Johnson RE. Transferring methadone-stabilized pregnant patients to buprenorphine using an immediate release morphine transition: an open-label exploratory study. AM J Addict 2006; 15:61-70.

Kahila, H, Saisto T, Kivitie-Kallio S, Haukkamaa M, Halmesmaeki E. A prospective study on buprenorphine use during pregnancy: Effects on maternal and neonatal outcome. Acta Obstet Gynecol Scand 2007a;86(2):185-190.

Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug and Alcohol Dependence 2008;96:69-78.

Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trail. Lancet 2003; 361:662-668.

Kahila H, Kivitie-Kallio S, Halmesmaeki E, Valanne L, Autti T. Magnetic resonance imaging of infants exposed prenatally to buprenorphine. Acta Radiol 2007b;48(2)228-231.

Kayemba-Kay's S, Laclyde JP. Buprenorphine withdrawal syndrome in newborns; a report of 13 cases. Addiction 2003;98:1599-1604.

Kurta DL, Krenzelok EP. A retrospective review of unintentional pediatric bupernorphine ingestions reported to a regional poison center. Clin Toxicol 2008;46(7):596.

Lacroix I, Berrebi A, Chaumerliac C, Lapeyre-Mestre M, Montastruc JL, Damase-Michel C. Buprenorphine in pregnant opioid-dependent women: first results of a prospective study. Addiction 2004;99:209-214.

Lejeune C, Aubisson S, Simmat-Durand L, Cneude F, Piquet M, Gourarier L; Groupe d'Etudes Grossesse et addictions. Withdrawal syndromes of newborns of pregnant drug abusers maintained under methadone or high-does buprenorphine: 246 cases. Annales de Medecine Interne 2001;152, Suppl 7:21-27.

Longfellow C. Office-based opioid addiction treatment and the rise in unintentional pediatric buprenorphine ingestions reported to a regional poison center – a new challenge for poison educators. Clin Toxicol 2008;46(7):634.

Loustauneau a, Auriacombe M, Daulouede JP and Tignol J. Is buprenorphine a potential alternative to methadone for treating pregnant drug users? Inventory of clinical data in the literature. Ann Med Int 2002; 153:2S31-2S36.

Lofwall MR, Stitzer ML, Bigelow GE, Strain EC. Comparative safety and side effect profiles of buprenorphine and methadone in the outpatient treatment of opioid dependence. Addict Disorder Therapeutic Treatment 2005; 4:49-64.

McCance-Katz EF, Moody DE, Morse GD, Friedland G, Pade P, Baker J, et al.Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside Reverse-transcriptase inhibitors efavirenz and delavirdine. Clin Infect Dis 2006a;43(4):S224-S234

McCance-Katz EF, Moody DE, Smith PF, Morse GD, Friedland G, Pade P, et al. Interactions between buprenorphine and antiretrovirals II. The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. Clin Infect Dis 2006b;43:S235-S246.

McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend 2007;91:269-278.

McKeown, NJ, West PL, Hendrickson RG. Persistent toxicity after Suboxone ingestion in a toddler. Clin Toxicol 2008;46(7):619.

Noblet, C. et al. Liver Injury caused by high dosage buprenorphine (HDB, Subutex): a national investigation by the French pharmacovigilance system (Abstract). Fundam Clin Pharmacology 2002; 16:417.

Ross D. High does buprenorphine in pregnancy. Aust NZ J Obstet Gynaecol 2004;44:80.

Schindler SD, Eder H, Ortner R, Rohrmeister K, Langer M, Fischer G. Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy. Addiction 2003;98:103-110.

Strengell P, Vahtola M, Tammela O, Seppa JK. Buprenorphine treatment during pregnancy: risk and advantages need to be carefully considered. Duodecim 2005;121:392-399.

Sullivan LE, Barry D, Moore BA, Chawarski MC, Tetrault JM, Pantalon MV,O'Connor PG, Schottenfeld RS, Fiellin DA. A trial of integrated buprenorphine/naloxone and HIV Clinical Care . Clinical Infect Dis 2006 Dec 15;43 Suppl 4:S184-S190.

Truitt C, Majlesi N, Greller H, Chan G, Lee D, Su M. Buprenorphine-induced respiratory depression reversed by naloxone in a 2-year old. Clin Toxicol 2008;46(7):604.

Yassen, A, et al, Pharmacokinetic-Pharmacodynamic Modeling of the Effectiveness and Safety of Buprenorphine and Fentanyl in Rats, Pharmaceutical Research, Vol 25, No. 1, Jan 2008, p 183-193

Zuin M. et al. Acute liver and renal failure during treatment with buprenorphine at therapeutic dose. Dig Liver Disorder 2008 Feb 20; 1-3.

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

/s/

Elizabeth M Kilgore
6/17/2009 05:14:09 PM
MEDICAL OFFICER

Celia Winchell
6/17/2009 05:30:39 PM
MEDICAL OFFICER
Concur