

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022410Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 8, 2010

To: Bob Rappaport, MD, Division Director
**Division of Anesthesia and Analgesia
Products (DAAP)**

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team
Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Product Information Reviewer
Division of Risk Management

Subject: Addendum to DRISK Review of Patient Labeling
(Medication Guide), dated August 6, 2009

Drug Name(s): Suboxone (buprenorphine and naloxone)
sublingual film

Application Type/Number: NDA 22-410

Applicant/sponsor: Reckitt Benckiser Pharmaceuticals Inc.

OSE RCM #: 2010-970

1 INTRODUCTION

This review is written as an addendum to the Division of Risk Management (DRISK) review of the MG for Suboxone (buprenorphine and naloxone) sublingual film, originally requested by the Division of Anesthesia and Analgesia Products (DAAP), and completed on August 6, 2009.

Please let us know if DAAP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

Draft Suboxone (buprenorphine and naloxone) sublingual flim Medication Guide (MG) submitted on October 20, 2008, revised by DRISK on August 6, 2009, and further revised by the review division and provided to DRISK on May 14, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

After the original MG review was completed on August 6, 2009, DAAP sent the Applicant a Complete Response (CR) letter on August 21, 2009 because the proposed REMS was not sufficient to ensure that the benefits of suboxone sublingual film outweigh the risks associated with the use of the drug. DRISK revisions of the MG from August 6, 2009 were not provided to the Applicant. We received comments from DAAP on May 14, 2010 in response to our MG review completed on August 6, 2009. These comments and revisions are the subject of this review addendum.

Our annotated MG is appended to this memo. We retained all of our previous comments as well as the comments from DAAP in the tracked changes version of the MG.

Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22410	ORIG-1	RECKITT BENCKISER PHARMACEUTICA LS INC	SUBOXONE (BUPRENORPHINE/NALOXONE) sublingual film

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

/s/

LATONIA M FORD

06/08/2010

Suboxone Addendum to DRISK Review of Patient Labeling (Medication Guide), dated August 6, 2009

MARY E WILLY

06/08/2010

I concur



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: August 6, 2009

To: Bob Rappaport, MD, Division Director
**Division of Anesthesia, Analgesia, and Rheumatology
Products (DAARP)**

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)
Jodi Duckhorn, MA, Team Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Product Information Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Buprenorphine and Naloxone (Suboxone)

Application
Type/Number: NDA 22-410

Applicant/sponsor: Reckitt Benckiser Pharmaceuticals INC.

OSE RCM #: 2009-2042

1 INTRODUCTION

This review is written in response to a request by the Division of **Anesthesia, Analgesia Rheumatology Product (DAARP)** for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Buprenorphine and Naloxone (Suboxone). Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Buprenorphine and Naloxone (Suboxone (b)(4)) Prescribing Information (PI) submitted, October 20, 2008 and revised by the Review Division throughout the current review cycle.
- Draft Buprenorphine and Naloxone (Suboxone (b)(4)) Medication Guide (MG) submitted on October 20, 2008 and revised by the review division throughout the review cycle.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

LATONIA M FORD
08/06/2009

JODI M DUCKHORN
08/06/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22410 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Suboxone Established/Proper Name: buprenorphine and naloxone Dosage Form: sublingual film Strengths: 8 mg / 2 mg and 2 mg / 0.5 mg		
Applicant: Reckitt Benckiser Pharmaceutical, Inc. Agent for Applicant (if applicable):		
Date of Application: October 20, 2008 Date of Receipt: October 21, 2008 Date clock started after UN:		
PDUFA Goal Date: August 21, 2009	Action Goal Date (if different): August 7, 2009	
Filing Date: December 20, 2008 Date of Filing Meeting: December 2, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3		
Proposed Indication(s): Maintenance treatment of opioid dependence		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): (b) (4) 75811	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aip.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempt (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i> If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments: This NDA is a "line extension" of an NDA (N20733) for sublingual tablets. The Sponsor is the same, and much of the underlying data is the same as was submitted under N20733, and was approved and granted orphan exclusivity.</p> <p>Because the Sponsor is the same as the previously approved product, the exclusivity for 20733 does not block exclusivity for 22410.</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>Note: <i>An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments: Although it does not appear that the Sponsor has specifically requested exclusivity, they do note that this product has been granted orphan designation.</p> <p>This Sponsor has previously been granted orphan exclusivity for another dosage form of this same combination.</p>	<input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO																
<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO																
<table border="1"> <thead> <tr> <th data-bbox="238 699 527 737">Application No.</th> <th data-bbox="527 699 805 737">Drug Name</th> <th data-bbox="805 699 1094 737">Exclusivity Code</th> <th data-bbox="1094 699 1385 737">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>		Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																	
<p>Format and Content</p>																	
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)																
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>																	
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p>If electronic submission, does it follow the eCTD guidance?</p>	<input checked="" type="checkbox"/> YES																

http://www.fda.gov/cder/guidance/7087rev.pdf	<input type="checkbox"/> NO
If not , explain (e.g., waiver granted):	

Form 356h: Is a signed form 356h included? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all establishments and their registration numbers listed on the form?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)	
If no , explain:	

Controlled substance/Product with abuse potential:	<input type="checkbox"/> Not Applicable
Abuse Liability Assessment, including a proposal for scheduling, submitted?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Consult sent to the Controlled Substance Staff?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

BLAs/BLA efficacy supplements only:	
Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If yes , BLA #	

Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

Debarment Certification	
Correctly worded Debarment Certification with authorized	<input checked="" type="checkbox"/> YES

signature? If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification. <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i> Comments:	<input type="checkbox"/> NO
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Field Copy Certification (NDAs/NDA efficacy supplements only)

Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>) <input type="checkbox"/> YES <input type="checkbox"/> NO
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Financial Disclosure

Financial Disclosure forms included with authorized signature? Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent. <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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Pediatrics

PREA <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	
Are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
If no , is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> If no, request in 74-day letter. If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), 	<input type="checkbox"/> YES <input type="checkbox"/> NO

(c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) Comments: orphan designated	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Prescription Labeling	
Check all types of labeling submitted. Comments: Also includes ancillary labeling components: Physician's Brochure, Pharmacists Brochure, and Patients Brochure.	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments: Although a MG wasn't submitted, the ancillary components were consulted to OSE with the request to assist in converting them into a MG.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable

Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
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Check all types of labeling submitted.	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
Comments:	
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

Meeting Minutes/SPA Agreements	
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End-of Phase 2 meeting(s) <i>If yes, distribute minutes before filing meeting.</i>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
Comments:	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
Comments:	

<p>Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p>	<p><input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO</p>
<p>Comments:</p>	

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 3, 2008

NDA/BLA #: 22-410

PROPRIETARY/ESTABLISHED NAMES: Suboxone (b) (4)

APPLICANT: Reckitt Benckiser

BACKGROUND: "Line extension" of the previously approved buprenorphine/naloxone sublingual tablets for the same indication.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Sullivan	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Celia Winchell		Y
Clinical	Reviewer:	Celia Winchell	Y
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		

Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xavier Ysern	Y
	TL:	Ali Al Hakim	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Rigo Roca, Deputy Division Director
Bob Rappaport, Division Director
Jim Hunter, CSS

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments: (see note below under Clinical)</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Has comments regarding certain data definition files.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Bob Rappaport</p> <p>GRMP Timeline Milestones: Provided to team</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

MATTHEW W SULLIVAN
08/04/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: July 08, 2009

To: Matthew Sullivan – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Through: Sam Skariah – Regulatory Review Officer
Michael Sauers – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-410 **TRADENAME[®] (buprenorphine/naloxone) sublingual**
film C-III for sublingual administration

DDMAC has reviewed the proposed product labeling (PI) and Medication Guide (Med Guide), for **TRADENAME[®] (buprenorphine/naloxone) sublingual film C-III** for sublingual administration, submitted for consult on March 5, 2009.

The following comments are provided using the updated proposed PI and Med Guide sent via email on July 2, 2009 by Matt Sullivan. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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

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

/s/

Mathilda Fienkeng
7/8/2009 06:05:16 PM
DDMAC PROFESSIONAL REVIEWER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: July 1, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Suboxone ^{(b) (4)} (Buprenorphine and Naloxone Soluble Film)
2 mg/0.5 mg and 8 mg/2 mg

Application Type/Number: NDA # 22-410

Sponsor: Reckitt Benckiser Pharmaceuticals Inc.

OSE RCM #: 2008-1807

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EXECUTIVE SUMMARY

Suboxone (b) (4) is a novel dosage form (sublingual strip) and a product line extension of Suboxone. Suboxone (b) (4) is identical to the currently marketed Suboxone sublingual tablets except for dosage form and the time it takes for the product to disintegrate in the mouth (3 minutes vs. 10 minutes). As such, the Division of Medication Error Prevention and Analysis (DMEPA) considered the vulnerability of the sublingual strip dosage form to cause error and considered the medication errors associated with the Suboxone sublingual tablets since these errors may be indicative of risks with Suboxone (b) (4). Also, DMEPA utilized Failure Mode and Effects Analysis¹ to evaluate the container labels, carton and insert labeling submitted by the Applicant to identify additional areas of vulnerability that could lead to medication errors.

Our Label and Labeling Risk Assessment findings indicate that improvements can be made to the presentation of the presentation of the established name, the graphic of the strip, the net quantity statement and the directions for administration on the container labels and carton labeling. We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for an assessment of the proposed container label, carton and package inset labeling for Suboxone (b) (4), for evaluation to identify areas that could lead to medication errors potential to contribute to medication errors.

Additionally, the Applicant submitted correspondence in the October 20, 2008 submission that listed the proposed benefits of the new dosage form and packaging. DMEPA evaluated the following five benefit claims that the Applicant submitted in this correspondence.

- Mitigation against unintentional pediatric exposure by providing child resistant packaging in a unit dose format.
- Protection against diversion by providing a dosage form that is more difficult to manipulate and conceal
- Provides a robust unit dose format for hospital and Institutional use
- Ease of use of the patient

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1.2 PRODUCT INFORMATION

Suboxone (b) (4) (Buprenorphine and Naloxone sublingual strip) are indicated for the maintenance treatment of opioid dependence. Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. Naloxone is an opioid receptor antagonist. Suboxone (b) (4) are available in strips that contain buprenorphine 2 mg and naloxone 0.5 mg; and buprenorphine 8 mg and naloxone 2 mg. The usual dose range is between 4 mg/1 mg to 24 mg/6 mg. The patient should place the specified number of strips under the tongue and allow to dissolve once daily. The strips should not be chewed, swallowed, or moved once placed under the tongue. The strips will be packaged in cartons containing 30 individual child resistant polyester/foil laminated pouches. Suboxone (b) (4) will be designated as a CIII controlled substance.

Suboxone is currently marketed as Suboxone sublingual tablets. Suboxone was approved on October 08, 2002, under NDA #20-733. The Applicant is proposing the introduction of a novel dosage form (sublingual strip) and will result in a product line extension of Suboxone. Suboxone (b) (4) and Suboxone sublingual tablets are identical in all product characteristics except for dosage form. The proposed Suboxone (b) (4) disintegrate more rapidly then compared to the currently marketed Suboxone sublingual tablets (3 minutes vs. 10 minutes). (b) (4)

2 METHODS AND MATERIALS

2.1 AERS DATABASE SEARCH FOR MEDICATION ERROR CASES

Since Suboxone is currently on the US market with the same active ingredients and indication for use, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the product which may be indicative of potential errors with Suboxone (b) (4).

The MedRA High Level Group Term (HLGT) “Medication Errors” and Preferred Term (PT) “Pharmaceutical product complaint” were used as search criteria for Reactions. The search criteria used for Products were a combination active ingredients search “bupren%” and “nalox%”, trade name “Subo%” and verbatim substance search “subox%”.

The cases were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. Those cases that did not describe a medication error or that did not describe an error applicable to this review (i.e. errors involving intentional overdose) were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. Our Division reviewed the cases within each category to identify factors that contributed to the medication errors, and to ascertain if these risks might apply to the proposed Suboxone (b) (4).

2.2 LABELS AND LABELING

This section describes the methods and materials used by DMEPA to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.²

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.³

Because our staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted container labels and carton labeling on June 8, 2009, and package insert labeling and correspondence stating the formulation and packaging benefits on October 20, 2008 for review (See Appendix A and B):

- Container label: 2 mg/0.5 mg and 8 mg/2 mg
- Carton labeling: 2 mg/0.5 mg and 8 mg/2 mg
- Package Insert Labeling (no image)
- Correspondence Stating Formulation and Packaging Benefits (no image)

3 RESULTS

3.1 MEDICATION ERROR CASES

For this review, DMEPA performed two searches of the FDA Adverse Event Reporting System (AERS) for medication errors submitted for Suboxone. The first search was conducted on November 25, 2008 and an updated search on February 1, 2009 to identify reports captured from November 25, 2008 through February 1, 2009. Collectively, the searches yielded a total of 57 reports.

² National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

After eliminating duplicate reports and reports that did not contain a medication error, 14 cases remained (see Appendix C). One of the 14 cases involved confusion between Suboxone tablets and enteric coated aspirin. This case was discussed in OSE Review #2008-1806 date January 13, 2008 and does not relate to this review, therefore this case was also excluded from further evaluation. Six of the remaining thirteen cases involved unintentional exposure to infants and pediatric patients, three of the thirteen cases involved wrong route of administration, and four of the cases involved confusion of the Suboxone strengths.

3.1.1 Unintentional Exposure to Infants and Pediatric Patients (n=6)

In all six cases of unintentional exposure to infants and pediatric patients, the children accidentally ingested Suboxone tablets. The patients' age ranged from 15 months to 24 months. All six children were hospitalized. Five cases reported difficulty breathing or respiratory arrest and the last case reported that the patient was difficult to arouse, had pinpoint pupils, and the patients eyes rolled back in their head. Of the 6 cases, four cases reported the patients required a naloxone intravenous drip, one patient required intubation, and one case did not give details on the corrective treatment provided. All six children recovered from the incidents. Only two cases reported the date of the event, both of those incidents occurred in 2007. The causes of the unintentional exposure were reported in 4 of the 6 cases. The reported cause in 3 cases was the child being left unattended with the medication, while the remaining case reported that the tablets were dropped on the floor.

3.1.2 Wrong Route of Administration (n=3)

Three cases of wrong route of administration were reported. The first case of wrong route of administration reported Suboxone tablets being crushed and then snorted. The event date and causality were unknown. The reported outcome was an adverse event of withdrawal symptoms.

The second case of wrong route of administration, reported in 2005, stated Suboxone tablets were found in the patient's stomach indicating that the patient either snorted or swallowed the tablets whole, but a definitive determination between the two routes could not be made. Causality was not reported and the reported outcome was death.

The last case of wrong route of administration occurred in 2006 and reported a patient injecting the medication intentionally. The outcome for this case was hospitalization.

3.1.3 Confusion of Strengths (n=4)

Two of the four cases that involved confusion of the strengths of Suboxone tablets were complaints that the presentation of the strength on the Suboxone labels was confusing. These cases were reported in 2003 and 2005. The first case indicated the similar labels and the lack of color differentiation as the source of the confusion and the second case stated that the presentation of the strength as the source of the confusion. Both of these errors did not reach the patient.

The final two cases reported in 2003 and 2004, involved the wrong strength of Suboxone being dispensed to patients. In both cases the prescriber wrote a prescription for "Suboxone 2 mg". In each case the pharmacist assumed the 2 mg was representative of the naloxone component in the higher strength tablet, instead of the buprenorphine component in the lower strength tablet. Only one case reported the outcome as difficulty breathing and dysphoria, but the patient recovered. Causality was reported in both cases as the strength not being well differentiated on the label, an incomplete prescription, and a knowledge deficit that more than one strength existed.

3.2 LABELS AND LABELING

Our review of the labels and labeling of Suboxone (b) (4) noted the following vulnerabilities that may contribute to medication errors:

3.2.1 *General Comments*

The graphic that appears above the proprietary name resembles a tablet.

The established name does not have the appropriate prominence as compared to the proprietary name. The Agency has determined that “sublingual film” is the appropriate dosage form for this product.

(b) (4)

The directions on the back of the label and labeling for utilizing the Suboxone (b) (4) can be revised to be easier to understand.

3.2.2 *Container Label*

The net quantity does not appear on the container labels.

3.2.3 *Carton Labeling*

The net quantity statement (b) (4) is confusing and can be revised to be easier to interpret.

3.2.4 *Package Insert Labeling*

No comments at this time.

4 DISCUSSION

As part of our analysis we evaluated 14 medication errors cases to determine if these cases would have an impact on the Suboxone (b) (4) container labels or the carton and package insert labeling. The relevant cases to this review involved confusion between the strengths of Suboxone tablets. However, the proposed labels and labeling minimize this potential for confusion and do not introduce any increased risk.

4.1 STRENGTH

Suboxone contains two active ingredients and the strength of each active ingredient appears on the principal display panel (2 mg/0.5 mg and 8 mg/2 mg). Each strength of Suboxone has an overlapping number (e.g. 2). Buprenorphine comes as 2 mg in the lower strength formulation and naloxone comes as 2 mg in the higher strength formulation. This overlap can cause confusion if prescribers do not specify the strengths of both components of the product since the 2 mg strength can refer to the buprenorphine or the naloxone component.

The proposed labels submitted by the Applicant for Suboxone (b) (4) clearly differentiates the strength of the two products by highlighting the strength of both components of the product in the upper right hand corner and using different colors on labels and labeling of the two strengths. The use of color differentiation and highlighting the strength of both active ingredients should help to minimize the errors related to wrong product selection. The use of color differentiation may help minimize errors related to selection errors, however highlighting the strength of both active ingredients on the label and labeling is unlikely to impact the risk of prescribers specifying the strength of only one active ingredient of Suboxone (b) (4)

Thus, there is still a risk that prescribers will only write the strength for one of the active ingredients of Suboxone (b) (4). This risk exists with the currently marketed Suboxone sublingual tablets and the introduction of Suboxone (b) (4) into the marketplace would not increase the risk of prescribers only writing the strength of one active ingredient. Additionally, the risk of a prescriber only writing the strength of one active ingredient when ordering Suboxone (b) (4) is minimized since Suboxone tablets have been on the market for 7 years and patients and healthcare providers are more familiar with the active ingredients of Suboxone. Furthermore, both of the previous cases that reported a medication error involving a prescription that only include a strength of one of the active ingredients of Suboxone tablets occurred within 2 years of the initial launch of Suboxone tablets.

4.2 LABELS AND LABELING

4.2.1 Graphic

The graphic that appears above the proprietary name (b) (4). Inclusion of this graphic is confusing because this product is sublingual film and Suboxone is also available as a tablet.

4.2.2 Established Name and Dosage Form Designation

The established name does not have the appropriate prominence as compared to the proprietary name per 21 CFR 201.10 (g)(2). Additionally, the Agency has determined that “sublingual film” is the appropriate dosage form for this product and the established name should reflect this determination.

4.2.3 Proprietary Name

(b) (4)

4.2.4 Administration Instructions

The directions for “taking Suboxone (b) (4) that appear on the contain/pouch label and carton labeling can be revised to be easier understood by patients. Patients using Suboxone (b) (4) may be confused by some of the word choices in the directions on the label and labeling.

4.2.5 Container Label

4.2.5.1 Net Quantity

The net quantity does not appear on the container label. The net quantity should appear on the label of a prescription drug per 21 CFR 201.51 (a).

4.2.6 Carton Labeling

4.2.6.1 Net Quantity

The net quantity statement is confusing. Healthcare practitioners and patients may interpret the current net quantity statement, (b) (4)

This confusion could result in error (b) (4)

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling risk assessment noted several areas of needed improvement. These revisions can be made prior to approval.

5.1 COMMENTS TO THE DIVISION

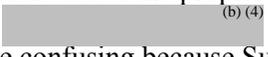
Suboxone sublingual film has been found to be more bioavailable than Suboxone sublingual tablets. Although DAARP has noted the difference in bioavailability for these products, the clinical significance of this difference has not been determined at this time and there is no description of this difference in the draft labels and labeling. If DAARP determines that the bioequivalence difference between these two products is clinically significant, DARRP may wish to consider using statements on the pouch labels, carton and insert labeling to alert healthcare practitioners and patients of this difference. DMEPA believes that lack of bioequivalence for these products can be successfully managed through label and labeling revisions.

We request that you convey our recommendations in section 5.2 to the Applicant. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, OSE project manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

We have evaluated your proposed labels and labeling and request that you revise the following prior to approval:

A. CONTAINER LABELS (1 STRIP)

1. Remove the graphic that appears above the proprietary name on both the container label and carton labeling. The graphic  is misleading because this product is a sublingual film and it may be confusing because Suboxone is also available as a tablet.
2. The established name is not the appropriate prominence compared to the proprietary name per 21 CFR 201.10 (g)(2). Increase the prominence of the established name by bolding the name or changing the font. Additionally, please note we made a final determination on the dosage form of the proposed product. The final dosage form of this product is “sublingual film” and the established name should be revised accordingly to reflect this decision.

3.



(b) (4)

4. Add the net quantity statement “1 sublingual film” to the container label.
5. Patients using Suboxone sublingual film may be confused by some of the word choices used in the directions. Revise all the instances of the phrase  to read “under the”. Revising this statement will make the directions more readily understandable to patients.

B. CARTON LABELING (30 STRIPS)

1. Healthcare practitioners and patients may interpret the current net quantity statement, (b) (4)

. Revise the net quantity statement (b) (4) to read “30 pouches each containing 1 sublingual film”.
2. Comments 1,2,3, and 5 listed for the Container Labels also apply to the Carton Labeling.

REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. *Reviews*

OSE Review #2008-1806 Proprietary Name Review for Suboxone^{(b) (4)} (Buprenorphine and Naloxone^{(b) (4)}), Oleszczuk, Z; January 13, 2009.

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

Appendix C: Summary of AERS cases related to Suboxone tablets.

ISR Number	Date Received	Medication Error Type	Narratives
4130739	06/03/2003	Wrong Strength	<p>My understanding is that a patient was prescribed Suboxone 2mg for 3 to 4 days. The pharmacist interpreted this dosage to refer to the naloxone component and therefore provided the patient with tablets that contained buprenorphine 8mg/naloxone 2mg. The patient experienced symptoms consistent with anxiety and withdrawal (my interpretation) and was instructed to by her physician to take 2 tablets instead of 1. She did so. When she realized the error the pharmacist had made she was concerned that she had received an overdose of the medication."</p>
4332050	03/31/2004	Wrong Strength	<p>This patient received the wrong dose of a medication called Suboxone. Part of the problem is the packaging. On the stock bottle of medication is written the word "Suboxone" and underneath, written in parenthesis, are the 2 drugs and their strengths: Suboxone -buprenorphine 8 mg and naloxone 2 mg- Suboxone - buprenorphine 2 mg and naloxone 0.5 mg - There is nothing that indicates that this drug comes in 2 strength. For instance, the name on each bottle says: Thyrolar-1, Thyrolar-2, Thyrolar -3 etc. on most combination products, both strengths are written in the name such as in "Lotrel 5/10", "Lotrel 10/20", etc. The doctor wrote this prescription for Suboxone 2. What makes this confusing is that there is 2 mg of one of the drugs in both strengths. Suboxone "2" contains 2 mgs of Buprenorphine: Suboxone "8" contains 2 mg of Naloxone. Neither of the bottles are labeled Suboxone "2" or Suboxone "8", both are labeled "Suboxone" with the ingredients below the name in an identical format. In our case we did not realize the drug came in 2 strengths. As one of the ingredients was 2 mg we assumed we ordered the correct product. I recommend the package label of Suboxone be changed immediately to list both strengths after the name : Suboxone 8/2 and Suboxone 2/0.5. In addition doctors should be warned to write prescriptions using the strengths of both medications, not just "Suboxone 2". In our case the patient had some temporary difficulty breathing and so dysphoria, but was otherwise unharmed. This could have been fatal had he followed the doctors instructions as written, which he did not. There is also the potential for a dispensing error even if the correct strength is chosen. The 2 package strenths are labeled almost identically and there is no scanning bar code on the bottle.</p> <p>Medication Error</p>
4923409	12/28/2005	Wrong Strength	<p>There was a report of a potential error involving Suboxone. There is a potential for confusion between the 2 mg and 8 mg products. The 2 mg strength is labeled SUBOXONE (buprenorphine 2 mg and naloxone 0.5 mg). The 8 mg strength is labeled SUBOXONE (buprenorphine 8 mg and naloxone 2 mg). Both labels have displayed '2 mg' on the front of the packaging</p>

			<p>which makes it confusing, and no strength appears immediately next to the brand name. The product labeling is poorly designed and that time after time, the staff has "pulled" the wrong strength to fill a prescription. No errors have reached a patient. There is also no barcoding on the bottles, which prevents them from using a barcoding system as an extra 'check' measure.</p> <p>The patient may be overdosed or underdosed.</p> <p>A contributing factor would be the confusing labeling of the products.</p>
5847611	08/147/2008	Wrong Drug	<p>Pharmacy dispensed Suboxone when enteric coated aspirin was prescribed -error in dispensing-. Patient had a prescription for EC aspirin refilled, noted that the pills looked unusual, but took what she thought was her normal dose. She felt dizzy and nauseated, and presented to a local emergency department. She will be observed and released with supportive care. Dispensing pharmacy is (b)(6). The pills dispensed were identified by imprint code--hexagonal, pink, scored on one side, "N8" on the other.</p> <p>Medication Error</p>
4126135	06/09/2003	Wrong Strength	<p>Suboxone 2mg and 8mg are packaged in the same size bottle with very similar labeling. The 2mg and the 8mg are not printed in a distinctive format ie raised or different color or some other way to differentiate between the two. This is true for both components of this drug. I am concerned that it would be easy to misread these labels and dispense the wrong strength.</p>
4993612	05/21/2006	Wrong Route of Administration	<p>Patient was instructed to take medication sublingually however, patient injected medication intravenously. Patient advised not to inject medication, rather, take as directed (sublingually).</p> <p>- Patient was admitted and treated for overdose. She was discharged home.</p> <p>- Patient has history of substance abuse.</p>
4749431	08/25/2008	Wrong Route of Administration	<p>Information from A. Bizzell, M.D. (SAMSHA) on 13-JUL-2005. The coroner's report (b)(6) from 6-JUN-2005 contains the following narrative information: The patient left mother's home to visit friend's house and stayed overnight. It is reported that he acted ill that night , while sleeping in a chair in living room. It is reported that he went outside and vomited. It is reported that in AM he was sleeping in a chair and snoring loudly; while all others in house allegedly went upstairs . It is reported that when they came down one hour later he was unresponsive. 911 was called but he was dead upon squad's arrival. Coroner's office was notified and responded - he was declared deceased by coroner @12:20 P.M. See autopsy report and (b)(6) Police Dept. investigative reports. Company called</p>

			<p>coroner's office (b) (6) (Toxicology) for attempt to find patient's prescribing MD. Both sources were unable to provide information. (b) (6) reports patient took friend's Suboxone - not his own prescription. (b) (6) referred Company to (b) (6) Police Dept. - (b) (6) - left voicemail message. Update 17-Aug-2005 Cause of death identified in coroners report as acute benzodiazepine and buprenorphine toxicity. Follow-up 19-AUG-2005: Report from (b) (6): In July 2005, I called (b) (6). His office was responsible for the post-mortem examination of a 20 year old Caucasian male who was found dead by an EMS team in (b) (6) after friends had found him unconscious. The date of his death was (b) (6). Forensic toxicology report found plasma levels of buprenorphine (3.4 ng/ml) Delta 9-tetrahydrocannabinol (6.3 ng/ml) and diazepam (0.10 ng/ml). The cause of death was given as drug toxicity (buprenorphine and diazepam). (b) (6) stated that an 8 mg tablet of Suboxone was found in the deceased's pocket as well as a small bag of cannabis. (b) (6) also informed me that there was buprenorphine in the stomach suggesting that the table had not been taken sub-lingually. Whether the drug was orally ingested or snorted (with some being washed down to the stomach) was impossible to ascertain. (b) (6) stated that he did not believe that the deceased was a "big time" drug user. He also informed me that the local police were conducting a criminal investigation to apprehend the individual(s) who gave or sold the deceased the drugs since he did not have a prescription for either Suboxone or diazepam. I called the (b) (6) police and was told that they could not give me any information until their investigation had been completed. On August 16th, 2005 I again contacted the (b) (6) Police Department but was unable to speak to the Chief of police. I will follow up on this and determine whether we can get the name of the deceased. If this is possible we will have our ethnographic team, under the direction of (b) (6), attempt to talk to the deceased's friends to determine more about his drug use history. From the buprenorphine plasma levels it would appear that the deceased was not significantly opioid tolerant.</p>
5382645	07/10/2007	Wrong Route of Administration	<p>Report No 1 from (b) (6) received 06-Jul-2007 (CIOMS dated 27-Jun-2007, ref 2007SP012982) This spontaneous report was received from a drug worker and concerns a male patient (demographics unknown) who on an unspecified date crushed a Suboxone (Buprenorphine/Naloxone) tablet and snorted the ingredients. Soon after, the patient experienced precipitated withdrawal. It was reported that the patient was also known to snort Subutex. (b) (6) considered the event of precipitated withdrawal to be serious.</p>
5674962	02/25/2008	Unintentional Exposure to Infant or	<p>Report No 1 received via Literature on 20-Apr-2007; A 16-month-old, 10-kg boy was found by his parent "making funny</p>

		Pediatric Patients	<p>faces." Approximately half a Suboxone tablet (buprenorphine 2mg/naloxone 0.5mg) was found in his mouth and another tablet was unaccounted for. The tablets belonged to his mother's partner, who had left her daily dose unattended. After the parent contacted the poison control center, she took the child to a local hospital. He arrived -45 minutes after the exposure. His presenting vital signs were: heart rate, 133 beats per minute; respiratory rate, 36 breaths per minute; temperature, 97.8F; and oxygen saturation, 98% on room air. He was somnolent and had miotic pupils on arrival. Approximately 1 hour after ED presentation his respiratory rate decreased to 15 breaths per minute, and he became more difficult to arouse. He received 3 boluses of 0.1 mg/kg intravenous naloxone over 105 minutes for recurrent respiratory depression, and he was transferred to a tertiary pediatric hospital. There, he initially appeared well but developed recurrent respiratory depression (respiratory rate; 10 breaths per minute with oxygen saturations of 92%) at hours 8 and 18 after the exposure. On both occasions he received naloxone 0.1mg /kg with full reversal. He underwent additional uneventful serial examinations and was discharged 30 hours after the exposure. Urine concentrations of buprenorphine and norbuprenorphine were 19 and 200 <i>ng/mL</i>, respectively. Corrective Treatment:</p> <p>Naloxone given intravenously and infant was monitored overnight.</p>
5674963	02/25/2008	Unintentional Exposure to Infant or Pediatric Patients	<p>Report No 1 received via Literature on 20-Apr-2007: A 22-month-old, 11-kg girl presented to the ED after ingestion of 1 tablet of Suboxone (buprenorphine 8mg/naloxone 2 mg) that belonged to a relative. Her family transported her to the ED after she became difficult to arouse and her eyes "rolled back." On presentation, her vital signs were: temperature, 97.9F; heart rate, 124 beats per minute; respiratory rate (reported), 20 breaths per minute; oxygen saturation, 98% on room air; and blood pressure, 101/69 mm Hg. Her physical examination, was unremarkable except for somnolence and miotic pupils. Intravenous naloxone 0.8mg (0.072mg/kg) produced improvement in her level of consciousness. After ~30 minutes, the patient again became lethargic. She then was started on a continuous infusion of naloxone at 0.5mg/hour and transferred to a PICU for further management. She remained easily arousable on the naloxone infusion during the course of her PICU stay. The naloxone infusion was discontinued 25 hours after the exposure, and she was discharged on the second hospital day. Corrective Treatment;</p> <p>Naloxone given as intravenous injections, then continuous intravenous infusion.</p>
5141722	02/25/2008	Unintentional Exposure to Infant or Pediatric Patients	<p>Report No 1 from Literature received 06-Oct-2006.</p> <p>Ann-Jeannette Geib, Kavita Babu, Michele Burns Ewald,</p>

			<p>Edward W.Boyer. Adverse Effects in Children After Unintentional Buprenorphine Exposure. Pediatrics 2006; 118 ; 1746 - 1751.</p> <p>Abstract : Buprenorphine in sublingual formulation was recently introduced to the American market for treatment of opioid dependence. We report a series of 5 toddlers with respiratory and mental status depression after unintentional buprenorphine exposure. Despite buprenorphine's partial agonist activity and ceiling effect on respiratory depression, all children required hospital admission and either opioid-antagonist therapy or mechanical ventilation. Results of routine urine toxicology screening for opioids were negative in all cases. Confirmatory testing was sent for 1 child and returned with a positive result. The increasing use of buprenorphine as a home - based therapy for opioid addiction in the United States raises public health concerns for pediatric population.</p> <p>A 16 16 - month old, 12.5 kg boy was found with a Suboxone tablet (buprenorphine 8 mg/naloxone 2 mg, prescribed for his father) in his mouth. Three hours later a caregiver found him unresponsive ; 2 hours after that, he was frothing at the mouth. On emergency medical services arrival, nearly 5 hours after ingestion, he was 'gaspng' (with a respiratory rate of 2 breaths per minute and blood pressure of 60 mm Hg systolic) and was promptly intubated. On arrival at the emergency department (ED) his blood pressure was 124/44 mm Hg, his heart rate was 144 beats per minute, and his respiratory was 24 breaths per minute on mechanical ventilation. The physical examination was significant for pinpoint pupils. He remained intubated overnight. His mental status improved, and he was extubated on the second hospital day. The remainder of his hospitalization was uneventful, and he discharged on the third day. Corrective Treatment: Intubated and mechanical ventilation.</p>
5674964	02/25/2008	Unintentional Exposure to Infant or Pediatric Patients	<p>Report No 1 was received via Literature on 20-Apr-2007: A 15-month-old, 12.7-kg boy presented to the ED with drowsiness. He had been found with orange pill residue in his mouth and on his hands. A family friend who was visiting the home was known to have dropped a Suboxone tablet (buprenorphine 8mg/naloxone 2mg) -30 minutes earlier. At the ED, the boy had pinpoint pupils and drowsiness. After receiving a total of 0.4mg naloxone in divided dose (0.016 mg/kg per dose) he became more arousable and had 1 episode of emesis. He was transferred to a tertiary care pediatric hospital and underwent 'serial examinations. During overnight monitoring he was noted to have desaturations to 91% while sleeping without depression in" respiratory rate. The next morning he was awake and playful and had stable vital signs. He was discharged to home that day. Corrective Treatment;</p> <p>Naloxone given intravenously times 2 doses and infant was monitored overnight.</p>

5675204	02/25/2008	Unintentional Exposure to Infant or Pediatric Patients	<p>Report no 1 received 16-oct-2007 Physician reports accidental ingestion of Suboxone 16 mg by 2 year old. The Child was air lifted to (b) (6) from his local Emergency department. Per the clinical liason's IPAQ report, :the child's stomach was pumped and charcoal was given and the child is now reportedly doing fine". A message has been left with (b) (6) offices in an attempt to get more information on this case. Report no 2 received 18-OCT-2007 Spoke with Patietns mother who provided clarification and additional information on this case. States Suboxone 8 mg tablets were unsecured in vehicle. Two year old son climbed into font seat of vehicle and discovered the Suboxone. He placed one 8 mg tablet in his mouth amd began to chew. Mother was able to sweep some of the pill fragments from the patient's mouth. About 5 minutes later patient begane to become very sleepy. Mom states his eyes were rolling in the back of his head and his pupils were pinpoint. Patient was immediately drive to the emergency department (a 15 minutes drive). Where he was evaluated, given narcan and medflighted to (b) (6) hospital where he was admitted to the pediatric intensive care unit. The patient remained on a narcan drip until (b) (6). He was dischated from the hospital on (b) (6). Mom states patient remained moody and agitated until the (b) (6).</p> <p>Corrective Treatment:"The child's stomach was pumped and charcoal was given' (b) (6); Child treated with Narcan.</p>
5675048	02/25/2008	Unintentional Exposure to Infant or Pediatric Patients	<p>Report No 1 received <i>via</i> Clinical Liaison on 26-Nov-2007: As reported, 18 month old boy took half of an 8mg Suboxone tablet by accident. He was "coded" but was okay after time spent in the emergency room. No further details known at this time. Follow-up received via telephone call on 30-Nov-2007: (b) (6) accidentally ingested Suboxone 4mg on (b) (6). While in the emergency room he stopped breathing. Reporter does not know the details of treatment as she states she was not <i>in</i> the room. (b) (6) was transferred to the Intensive Care Unit where he was observed overnight, had no further adverse effect and was discharged the next morning on (b) (6). No further details available.</p> <p>Corrective Treatment;Infant was "coded" (details unknown) and observed overnight in the intensive care unit.</p>

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/s/

Zachary A Oleszczuk
7/1/2009 01:22:14 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
7/1/2009 01:42:17 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/1/2009 03:48:44 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/2/2009 08:55:49 AM
DRUG SAFETY OFFICE REVIEWER



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 26, 2009

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: JianPing (John), M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA 22-410, Suboxone (b)(4)[®] (buprenorphine and naloxone soluble film)
Indication: Treatment of opioid dependence
Dosages: 8 mg/2 mg, 2 mg/0.5 mg, sublingual administration
Company: Reckitt Benckiser

Materials reviewed: NDA 22-410 is located in the EDR.

Submission:

This memorandum responds to a consultation from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) to the Controlled Substance Staff (CSS) regarding the abuse and diversion potential of Suboxone strips (buprenorphine and naloxone soluble film).

I. Summary:

The Sponsor submitted a 505(b) (1) submission for 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, and was developed as an alternative to Suboxone sublingual tablets (NDA 20-733, approved October 8, 2002). The Suboxone (b)(4)[®] was developed to improve and shorten the oral residence time of the currently marketed Suboxone sublingual tablets using soluble film technology. Compared to the tablets, the film formulation provides reduced oral residence time (tablet disintegration time up to 10 minutes versus 3 minutes for the film). 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 / naloxone 2mg; buprenorphine 2mg / naloxone 0.5mg). The target daily dose is 16 mg/4 mg.

The Sponsor contends that the soluble film dosage would protect against diversion by providing a dosage form that is very difficult for the subject to remove from the sublingual or buccal

mucosa after administration and it would provide the potential advantages over the current Suboxone (buprenorphine and naloxone) product. The Sponsor claims that the soluble film dosage form would provide a number of improvements including:

- Use of child-resistant packaging in unit dose format
- Protection against counterfeiting
- Protection against illegal diversion
- 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

II. Background

In the 1980s, buprenorphine hydrochloride was first marketed as an analgesic by Reckitt & Colman (now Reckitt Benckiser) as Buprenex in a 0.3 mg/ml injectable formulation. In October 2002, FDA additionally approved Suboxone and Subutex, buprenorphine's high-dose sublingual pill preparations for treatment of opioid addiction in physicians' office practices (pursuant to provisions of the Drug Addiction Treatment Act (DATA) passed by Congress in 2000). Subutex and Suboxone are available in 2 mg and 8 mg sublingual dosages. Until that time, methadone was the only approved treatment for opioid addiction which could only be prescribed in licensed methadone treatment clinics.

III. Conclusions

NDA 22-410 includes no new efficacy studies. It includes 18 Phase I pharmacokinetic (PK) studies designed to obtain information about bioavailability, bioequivalence and dose proportionality. Although there were differences in the relative exposures of naloxone to buprenorphine for the film formulation relative to the tablet (10-25% less for the 2mg/0.5 mg and 4 mg/1mg doses), the Sponsor concludes that the two formulations are comparable according to PK parameters and equivalent in effectiveness for treating opioid dependence. In addition, the NDA includes a Phase II safety and tolerability study (RB-US-07-0001) developed to demonstrate adequacy of transition from the tablet to the film formulation and to provide supportive safety-related data.

Based on our review of RB-US-07-0001 and other data, CSS finds that:

- As an open label, uncontrolled clinical study, RB-US-07-0001 provides us some safety information but does not provide evidence to compare the safety profile of the Suboxone strip to the Suboxone tablet.
- Our analysis is a retrospective analysis of data previously collected, rather than a prospective evaluation where procedures and criteria were defined prior to conduct of the study.
- There is a lack of evidence that the clinical investigators received appropriate training in the identification and coding of relevant behaviors (misuse, abuse, addiction, other aberrant behaviors, diversion, etc.).
- That being stated, events observed in the clinical trial illustrate the significant risks of abuse and diversion from Suboxone strip. We recognize that this drug is being developed for treatment of a patient population of individuals who are addicted to opiates. As such,

the detection of aberrant drug use behavior in the setting of a clinical trial, though typically unusual, is often expected in this group. Nevertheless, concern for the use of this drug by patients is a safety concern.

- We note a high incidence of drug unaccountability in subjects who completed the trial and those who were discontinued in each of the three clinical sites. This is predictive of the likely occurrence of diversion after the drug is approved and marketed.

Taken together, these findings suggest that expanded use of this product will result in significant abuse and diversion that needs to be considered with any anticipated benefits the drug may offer.

IV. CSS Review

Buprenorphine is a synthetic opiate and produces the euphoric effects sought by opiate abusers; therefore, it is susceptible to abuse and diversion. This review is limited to issues concerning the potential abuse and diversion of Suboxone. Information included in this review includes general summary data provided by the sponsor, PK summary from clinical pharmacology interim review, and CSS independent analysis of the original data.

1. Safety of Suboxone (b) (4)

Sublingual administration results in rapid delivery and enhanced absorption of buprenorphine. Suboxone film represents a new formulation of buprenorphine that allows rapid absorption of drug that result in rapid high plasma levels. Suboxone® film was developed to improve and shorten the oral residence time of the currently marketed Suboxone sublingual tablets using soluble film technology. Compared to the tablets, the film formulation provides reduced oral residence time (tablet disintegration time up to 10 minutes versus 3 minutes for the film)

In bioequivalent study, the relative bioavailability of buprenorphine and naloxone in different formulations (film strip and tablet) of Suboxone has also been studied, and it is indicated that both of buprenorphine and naloxone in Suboxone film has a significantly higher bioavailability than the Suboxone tablet, as demonstrated by C_{max} , AUC_{last} and AUC_{inf} values, with % Ratio (Test/Ref) of about 120% (Tables 1 and 2 from Clinical Pharm interim review).

Table 1. BE study linking the 2/0.5 mg film strip to the tablet: Study 20-250-SA
(Source: Clinical Pharm. Midcycle Meeting Slides)

Parameters	Geometric Mean ^a		% Ratio ^b	90% CI		Power	CV%
	Test ^c	Ref ^c	(Test/Ref)	Lower	Upper		
Buprenorphine							
ln (C_{max}), n=41	0.8617	0.7083	121.66	112.62	131.43	0.9986	20.93
ln (AUC_{last}), n=41	7.3144	6.2841	116.40	108.70	124.63	0.9998	18.48
ln (AUC_{inf}), n=38	8.2642	7.2355	114.22	106.65	122.32	0.9997	17.78
Naloxone							
ln (C_{max}), n=41	48.5861	46.7142	104.01	95.79	112.93	0.9968	22.33
ln (AUC_{last}), n=41	120.6273	118.4493	101.84	94.84	109.36	0.9995	19.26
ln (AUC_{inf}), n=23	123.5046	115.1191	107.28	96.98	118.69	0.9750	20.02

Table 2. BE study linking the 8 mg/2 mg film strip to the tablet: Study 20-273-SA
(Source: Clinical Pharm. Midcycle Meeting Slides)

Parameters	Geometric Mean ^a		% Ratio ^b	90% CI		Power	CV%
	Test ^c	Ref ^c	(Test/Ref)	Lower	Upper		
Buprenorphine							
ln (C _{max})	3.0333	2.3735	127.80	116.11	140.66	0.9845	27.16
ln (AUC _{last})	26.4773	22.0360	120.15	110.24	130.96	0.9947	24.31
ln (AUC _{inf})	28.3228	23.6995	119.51	110.28	129.51	0.9976	22.66
Naloxone							
ln (C _{max}), n=44	175.5140	124.4383	141.04	126.87	156.80	0.9652	30.12
ln (AUC _{last}), n=44	423.7415	325.8478	130.04	119.51	141.50	0.9957	23.83
ln (AUC _{inf}), n=24	445.5786	367.6626	121.19	108.44	135.44	0.9512	22.62

2. Limitations of the Clinical Study RB-US-07-0001

Clinical Study RB-US-07-0001 is “A Phase 2, Multi-Center, Open-Label Study to Assess the Safety and Tolerability of a Buprenorphine/Naloxone Film Strip Administered by the Sublingual and Buccal Routes”. A total of three investigation sites were initiated in the United States. A total of 382 subjects were enrolled and 249 subjects completed the study.

Subjects were randomly assigned to one of two dosing regimens: (1) **sublingual** administration of the buprenorphine and naloxone soluble film for 12 weeks or (2) **buccal** administration of the buprenorphine and naloxone soluble film for 12 weeks.

According to the Sponsor, the results of the study demonstrated that opioid treatment with the strip formulation, administered sublingually or buccally, up to 12 weeks, is safe and well-tolerated. The Sponsor concluded that there were no clinically meaningful differences identified between the two groups. The overall incidence of AEs was similar and there were no deaths or treatment related serious adverse events. The Sponsor asserts that only 8 subjects were discontinued from the study due to AEs.

After review of the clinical study report and database for the study RB-US-07-0001, our overall conclusion is that the study was poorly designed and conducted and was not useful for demonstrating any difference in the safety profile or abuse potential of the two formulations. This conclusion is based on the following limitation of the study:

- There was no positive control arm (Suboxone tablet group) in this study. So, it would be impossible to claim any potential advantages of Suboxone strip over the current Suboxone tablet product.
- There was a high discontinuation rate. Among 382 randomized subjects, 121 of them discontinued and the overall discontinuation rate was 31% (Table 3). The discontinuation rate at Site 777 was 63% (Table 3).

Table 3. Summary of Disposition of Subjects

Site	Randomized	Completed	Discontinued
111	122	77(63%)	41(34%)
333	233	163(70%)	62(27%)
777	27	9(33%)	17(63%)
Total	382	249(65%)	120(31%)

- From our analysis, there appears to be some problems in assuring the quality of the data. For example, by joining the dataset DISP.jump (amount of drug dispensed) with dataset STDG.jump (amount of drug returned), it showed that there were as many as 57 subjects returning more films than what they were apparently given overall. This is very difficult to reconcile. Another example in the study is Sponsor provided Tab 14.6.1.14 Treatment Compliance. The Treatment Compliance was 106.8 overall. However, all individual visits Treatment Compliance were less than 100, ranging from 82.8 to 98.2.
- There was no common standard across sites for carrying out urine drug screens. The urine drug screen for drugs of abuse was performed according to the local study centers' standard of care. Thus, the analytes being tested may have varied from site to site. Furthermore, the percentage of subjects who completed the buprenorphine test at some visits is very low. For example, no one completed the test at visit 2 at Site 333 and only 33% of subjects completed at visit 8 at Site 777 (Table 4).

Table 4. Summary of Subjects who completed Urine Buprenorphine Screen

Site	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
111	100%	100%	89%	84%	82%	74%	71%	67%	86%	84%
333	100%	0	91%	88%	85%	81%	78%	75%	87%	75%
777	93%	100%	96%	93%	85%	89%	78%	33%	85%	82%

3. Drug Diversion and Abuse Potential

Analysis of All Subjects in Clinical Trial RB-US-07-0001

During the clinical trial RB-US-07-0001, drug unaccountability of Suboxone film from the study centers were reported by the Sponsor. We calculated the percentage of the drug that should have been returned that is missing (Table 5). The report showed that there was a substantial amount of drug unaccounted for (overall 46%), with a totally of 6,008 suboxone film strips missing. The precise number of missing film strips is difficult to substantiate.

Table 5. Overall drug accountability in RB-US-07-0001 (Calculated by data from the Sponsor - NDA 22-410).

Site	Film dosage strength	Quantity dispensed	Quantity prescribed	# films returned	# of films that should have been returned	# films missing	% of films that should have been returned that is missing
111	2mg/0.5mg	8,674	6,753	1,162	1,921	759	40%
111	8mg/2mg	6,862	5,411	773	1,451	678	47%
111	12mg/3mg	173	97	35	76	41	54%
111	16mg/4mg	207	155	33	52	19	37%
total 111	all	15,916	12,416	2,003	3,500	1,587	43%
333	2mg/0.5mg	3,020	2,412	459	608	149	25%
333	8mg/2mg	13,687	10,621	2,053	3,066	1,013	33%
333	12mg/3mg	11,490	9,283	1,221	2,207	986	45%
333	16mg/4mg	8,917	7,086	1,080	1,831	751	41%
total 333	all	37,114	29,402	4,813	7712	2899	38%
777	2mg/0.5mg	3,213	2,513	86	700	614	88%
777	8mg/2mg	4,210	3,338	59	872	813	93%
777	12mg/3mg	146	112	0	34	34	100%
777	16mg/4mg	448	366	21	82	61	74%
total 777	all	8,017	6,329	166	1688	1522	90%
Total all sites	2mg/0.5mg	14,907	11,678	1,707	3,229	1,612	47%
Total	8mg/2mg	24,759	19,370	2,885	5,389	2,504	46%
Total	12mg/3mg	11,809	9,492	1,256	2,317	1,061	46%
Total	16mg/4mg	9,572	7,607	1,134	1,965	831	42%
Total all sites	all dosages	61,047	48,147	6,982	12,900	6,008	46%

Analysis of Subjects discontinuing Clinical Trial RB-US-07-0001

CSS requested the Sponsor to submit the narratives of discontinued subjects in RB-US-07-0001. Analysis of the narratives of 79 discontinued subjects in study 001 suggested a dramatic potential for buprenorphine diversion: 59 (74%) of them failed to return strips. These subjects possessed 1,346 strips with over 10 g of buprenorphine when they withdrew from the study (Table 6 and 7). The sublingual arm showed a higher incidence of drug missing than buccal arm.

Table 6. Drug accountability of discontinued subjects in sublingual arm of RB-US-07-0001

	Total Subject #	Failed to Return Strips	# of Strips not Returned	Buprenorphine not Returned (mg)
Investigator Decision	10	7 (70%)	146	1548
Protocol Violation	2	2 (100%)	36	424
Lost to Follow Up	18	18 (100%)	501	4800
Others	17	11 (65%)	179	1044
TOTAL	47	38 (81%)	862	7816

Table 7. Drug accountability of discontinued subjects in buccal arm of RB-US-07-0001

	Total Subject #	Failed to Return Strips	# of Strips not Returned	Buprenorphine not Returned (mg)
Investigator Decision	13	6 (46%)	100	644
Protocol Violation	2	2 (100%)	8	16
Lost to Follow Up	13	11 (85%)	367	1534
Others	4	2 (50%)	9	112
TOTAL	32	21 (66%)	484	2306

The analysis of 58 fixed dosing subjects indicated that 8 mg/2 mg was the most common missing packet (Table 8). The overall drug accountability of discontinued subjects in RB-US-07-0001 is listed in Table 8.

Table 8. Overall drug accountability of discontinued subjects in RB-US-07-0001

Site	Film Dosage Strength	# of Missing Films	Buprenorphine missing (mg)
111	2mg/0.5mg	79	156
111	8mg/2mg	112	896
111	12mg/3mg	17	204
TOTAL	All	208	1253
Site	Film Dosage Strength	# of Missing Films	Buprenorphine missing (mg)
333	2mg/0.5mg	34	68
333	8mg/2mg	188	1296
333	12mg/3mg	103	1220
333	16mg/4mg	50	800
TOTAL	All	375	3384
Site	Film Dosage Strength	# of Missing Films	Buprenorphine missing (mg)
777	8mg/2mg	177	1416
777	12mg/3mg	10	120
777	16mg/4mg	68	136
TOTAL	All	255	1672
	Film Dosage Strength	# of Missing Films	Buprenorphine missing (mg)
Total of all sites	2mg/0.5mg	133	224
Total	8mg/2mg	477	3608
Total	12mg/3mg	130	1544
Total	16mg/4mg	118	936
Total of all sites	all dosages	838	6309

This table only included the analysis of 58 fixed-dose subjects. 21 subjects with adjusting doses were not included

Analysis of Subjects Completing Clinical Trial RB-US-07-0001

Overall, 249 of 382 subjects (65%) completed the clinical trial RB-US-07-0001, These include both sublingual and buccal arms. The analysis of the database provided by the sponsor for “protocol deviation” indicated that there was also a high incidence of drug missing in the pool of completed subjects. See Table 9 (below) for the number (%) of completed subjects who were missing at least one film in the trial.

Table 9. Summary of missing films for completed subjects in clinical study RB-US-0001

Site	Total Subjects	Completed Subjects	Missing Film Subjects #	# Missing Films
111	122	77	75 (97%)	3257
333	233	163	109 (67%)	525
777	27	9	7 (78%)	150

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 15, 2009

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Drug Utilization Data Analyst
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Subject: Buprenorphine-related hepatic toxicity

Drug Name(s): Suboxone ^{(b) (4)} (buprenorphine/naloxone)

Application Type/Number: Initial NDA submission 22-140

Applicant/sponsor: Reckitt Benckiser

OSE RCM #: 2009-262

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EXECUTIVE SUMMARY

1 BACKGROUND

The Division of Anesthetic, Analgesia, and Rheumatology Products (DAARP) requests information regarding postmarketing liver toxicities related to use of buprenorphine. DAARP is currently reviewing a product (Suboxone strip) that contains buprenorphine and naloxone (NDA 22-410). The proposed indication is “maintenance treatment of opioid dependence.” Buprenorphine is a μ -opioid receptor partial agonist and a κ -opioid receptor antagonist. Naloxone is an opioid receptor antagonist that is poorly absorbed orally and which is included in the preparation to deter intravenous use.

In January of 2002, Martin Pollock, Pharm.D., of the Division of Drug Risk Evaluation conducted a safety review of hepatic toxicity reported in association with buprenorphine use, which was then only available as an intravenous injection. The review was prompted by a published study, “Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine” (Petry NM et al. Am. J. Addict. (2000) 9:265-269). Using the AERS High-Level Group terms “hepatic disorders (excluding neoplasms)” and “hepatobiliary investigations” and the preferred term “liver transplant” he found 24 unduplicated cases. Dr. John Senior also reviewed the postmarketing hepatic cases associated with buprenorphine (review dated May 2002). Many of the hepatic event cases were confounded, a fact that is reflected in labeling (see below).

The purpose of this review is to discern if the hepatic safety profile of buprenorphine-containing products is different from that reflected in labeling.

1.1 INTRODUCTION

1.2 REGULATORY HISTORY

Sublingual tablet formulations of buprenorphine and buprenorphine and naloxone were approved in the U.S. under NDA 20732 and 20733 on October 8, 2002, with a postmarketing commitment to study the safety of buprenorphine.

Reckitt Benckiser submitted NDA 22-410 for buprenorphine/naloxone sublingual strips (Suboxone (b)(4)) on October 20, 2008. The PDUFA goal data from the application is August 20, 2009.

1.3 PRODUCT LABELING

The proposed indication is “maintenance treatment of opioid dependence.” (b)(4)

(b)(4)

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

Criteria

The AERS data base was searched for all events reported up April 16, 2009. It included serious and nonserious cases, according to the following search criteria:

1) Products

- Active ingredient: buprenorphine, buprenorphine HCl, buprenorphine HCl H-3, buprenorphine-3B-D-glucuronide
- Trade name: Suboxone, Subutex

2) Adverse event terms.

- Hepatic and hepatobiliary disorders (High-level group term (HLGT))
- Hepatobiliary investigations (HLGT)
- Liver transplant (Preferred term, (PT))
- Liver and small intestine transplant (PT)
- Renal and liver transplant (PT)

The search included cases in the United States and elsewhere.

Duplicates were removed from the resulting 145 and an assessment was made as to whether cases fulfilled the OSE definition of severe liver toxicity or liver failure:

Category 1: Severe hepatotoxicity

- Reports with (ALT or AST $\geq 3x$ upper limit of normal, ULN) and bilirubin $\geq 3x$ ULN or jaundice or INR >1.5 or bleeding events. Hospitalization not required.
- Reports with any elevation of transaminases, if patient hospitalized
- Reports of bilirubin $\geq 3x$ ULN or jaundice due to liver injury, if patient hospitalized
- Reports of hepatitis, hepatotoxicity, or liver dysfunction with no lab data, if required hospitalization or reported death.

Category 2: Acute liver failure, fatal or non-fatal

- Interval from the development of liver-related signs/symptoms or jaundice to any of the following within a period of 3 months or less, or suggestive of a rapid time course: encephalopathy, coma, placement on a liver transplant list, liver transplantation, or death related to acute liver injury.
- Severe liver injury (ALT or AST $\geq 3x$ ULN) and bilirubin $\geq 3x$ ULN or jaundice or INR >1.5 or bleeding events accompanied by hepatorenal syndrome or renal failure with no other apparent etiology.
- Diagnosis of liver failure without supporting clinical or laboratory data.

2.2 LITERATURE SEARCH

PubMed was used for cases not reported in AERS.

2.3 ANALYSES

No statistical tests were performed.

3 RESULTS

3.1 ADVERSE EVENT CASES

The adverse event search yielded 145 reports, of which 22 were duplicates, yielding 123 cases.

Table 1 summarizes the reasons for exclusion from the case series. Reasons included:

1. Irrelevant: Did not report a new liver disease
2. Insufficient information to evaluate the condition or its severity
3. Insufficient severity to meet OSE definition
4. Overdose of buprenorphine or other drugs
5. Neonatal jaundice, hepatomegaly, and gray/yellow coloring
6. Another significant event or illness that was more likely responsible for liver toxicity. This included sepsis, drug withdrawal, Epstein-Barr virus infection, toxic epidermal necrolysis, shock, multiorgan failure from intravenous injection in an intravenous drug abuser, and fatty liver of pregnancy

Table 1. Reasons for exclusion from the case series

Category	N (total of 123)
Irrelevant	20
Insufficient information	26
Insufficient severity	17
Overdose	6
Neonatal	8
Significant illness	16
Total excluded	93

In the remaining 30 cases, buprenorphine may have contributed to the severe hepatic disorder.

Numerous cases (see Appendix 1, Table 2) had confounders:

- Patients with histories of hepatitis or cirrhosis or both: 16
- Patients taking concurrent medications labeled for hepatic affects: 14
- Patients with reported ongoing injection drug use: 3

In addition, there were 4 cases in which neither concomitant medications nor concurrent diseases were reported (including one in which the indication was pancreatic pain), and an additional one in which no confounding medication condition was reported, but a potentially confounding treatment was given (Table 3).

The age ranges of the 28 cases in which the age range was stated was 20-89 years. Where reported (20 cases), buprenorphine was used by persons with addiction or explicitly for narcotics substitution in 12 cases and for other indications (mostly pain relief) in 8 cases. Death due to liver failure was reported in 2 cases. Withdrawal of buprenorphine alone was associated with amelioration of the clinical syndrome or a return toward normal of biochemical hepatic laboratory tests in 5 cases.

This review shows that buprenorphine may exacerbate hepatic dysfunction or may sensitize the liver to further injury, but do not necessarily support a sole etiologic role for liver injury.

3.2 LITERATURE SEARCH

Reckitt Benckiser provided two reports from the literature:

1) Berson A et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. *J. Hepatol.* 34 (2001) 346-350. This article reports four cases of heroin addicts infected with hepatitis C, who experienced an increase in ALT to 13-50 times the upper limit of normal after IV injection of buprenorphine. "Interruption of buprenorphine injections was associated with prompt recovery, even though two of these patients continued buprenorphine by the sublingual route...A fifth patient carrying the hepatitis C and human immunodeficiency viruses, developed jaundice and asterixis with panlobular liver necrosis and microvesicular steatosis after using sublingual buprenorphine and small doses of paracetamol and aspirin." Two of these patients are reported in the case series (see Appendix 1).

2) Houdret N et al. Severe hepanonephritis and buprenorphine intoxication. *Acts Clinica Belgica* (1999) 51; 29-31. This is a case of overdose, reporting severe hepatitis, acute renal failure, and anuria. Normalization of hepatic and renal function was associated with discontinuation of buprenorphine and hemodialysis.

I searched PubMed by using Buprenorphine, Subutex, or Suboxone as title words, each combined with liver, toxicity, and hepatitis individually as title terms, or liver toxicity or hepatic toxicity as text terms. I did not restrict the search by date. I found no other relevant cases.

4 CONCLUSION

Buprenorphine may aggravate hepatic dysfunction or predispose to liver injury, but the data do not strongly support an etiologic role.

5 RECOMMENDATIONS

I recommend the following changes to labeling (**bolding** added):

(b) (4)

6 DRUG UTILIZATION REVIEW

Note: Drug utilization review, including the associated appendices, were provided by Patty Greene, Pharm.D.

6.1 DETERMINING SETTING OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Suboxone® and Subutex®. The examination of wholesale sales data for year 2008 indicate that both products were distributed primarily to outpatient retail pharmacy setting (chain stores, independent pharmacies, and food stores). Approximately 91% of Suboxone® and 89% of Subutex® bottles or packet of pills were distributed to outpatient retail pharmacy settings.^[1] Thus, we examined outpatient utilization patterns from January 2003 through December 2008. We examined total dispensed prescriptions for Suboxone® and Subutex® using SDI Vector One®: National (VONA). The total number of patients receiving a prescription for Suboxone® and Subutex® at a U.S. retail pharmacy was obtained from the SDI Vector One®: Total Patient Tracker (TPT). Database descriptions can be found in Appendix 2.

6.2 DRUG UTILIZATION DATA RESULTS: DISPENSED PRESCRIPTIONS AND PROJECTED PATIENTS

Table 1 in Appendix 2 displays the total number of prescriptions dispensed by age in the outpatient retail setting (mail order excluded) for Suboxone® and Subutex®. During the review period for years 2003-2008, approximately (b) (4) prescriptions were dispensed for Suboxone® and Subutex® in the United States. Suboxone® accounted for approximately (b) (4) of the total share. The number of Suboxone® dispensed prescriptions increased nearly 15-fold from roughly (b) (4) prescriptions in year 2004 to (b) (4) prescriptions in year 2008. Subutex® dispensed prescriptions increased 7-fold from (b) (4) prescriptions in year 2004 to (b) (4) prescriptions in year 2008.

There has been an increase in the number of prescriptions dispensed across all age groups for Suboxone® and Subutex® over the course of this review period. The age 26-35 year group accounted for the largest share of dispensed prescriptions for both Suboxone® and Subutex® with (b) (4) respectively.

Trends for patient data were similar to that of prescription data (Appendix 2, **Table 2**). For the entire study period, approximately (b) (4) patients received a prescription for Suboxone® ((b) (4) patients) or Subutex® (b) (4) patients) from outpatient retail pharmacies. Suboxone® held the majority of the market at (b) (4). Between year 2004 and 2008, the number of patients receiving a prescription for Suboxone® increased approximately 10-fold from (b) (4) patients to (b) (4) patients. The number of patients receiving a prescription for Subutex® increased 4-fold from (b) (4) patients to approximately (b) (4) patients during the same time period. Approximately (b) (4) of patients that received a prescription for Suboxone® were age 26-35 years followed by adults age 36-45 years with (b) (4). Pediatric patients ages 0-17 accounted for (b) (4) of the total patient volume for Suboxone® over the entire review period. Subutex® shared similar age distribution.

6.3 Drug Utilization Data Limitations

Drug utilization findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Suboxone® and Subutex® were distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the

^[1] IMS Health, IMS National Sales Perspectives™, Year 2008, Extracted 2-2009. Original File: 0902bupr.dvr.

facilities purchase drugs in quantities reflective of actual patient use. SDI's VONA provide estimates of the number of prescriptions dispensed through outpatient retail pharmacies in the United States, respectively. Mail order data was not provided and thus retail dispensed prescriptions may be underestimated.

6.4 Drug Use Conclusion

For the entire review period, (b) (4) prescriptions were dispensed for Suboxone® and Subutex® products to approximately (b) (4) patients in the United States. For the most recent 12-month period ending in December 2008, Suboxone® utilization accounted for over (b) (4) of the total share with approximately (b) (4) prescriptions and nearly (b) (4) patients in the outpatient setting. Subutex® accounted for (b) (4) prescriptions and (b) (4) patients for the same period.

7 APPENDICES

APPENDIX 1: TABULAR SUMMARIES OF ADVERSE EVENT CASES

Table 2. Cases of possible role of buprenorphine

Case qualification	Summary of case [AERS ISR number]
Possible prolongation of hospitalization	45 yo woman on 3rd day after cholecystectomy experienced SGPT 440U, SGOT 490U. Received buprenorphine, midazolam, phenergan, and other medications for procedure. [ISR 140540] midazolam: elevated transaminases
Hospitalization	Man of unreported age hospitalized for abnormal liver function test; liver biopsy showed "moderate fatty change and no evidence of inflammation or fibrosis." Concomitant medications included ibuprofen, diclofenac, dextropropoxyphene/paracetamol and dihydrocodeine/paracetamol for unreported indications. [ISR1753913]
Hospitalization	62 yo man with cirrhosis on buprenorphine and motilium for 2 days for unreported indications developed "hepatic comatose state" on the same day as cibacalcine onset; heptaminol HCl was given for unknown dates [ISR1781874]
Possible hospitalization	30 yo female with heroin abuse and hepatitis C injected Subutex daily; "hepatic enzymes being 56 times the normal range"; liver biopsy showed "signs of a toxic hepatitis." [ISR 3129442]
Hospitalization	27 year-old man with heroin addiction and chronic hepatitis C took Subutex tablets for 6 days; on 5th day AST was "60 N" and ALT was "130N". He was hospitalized; with discontinuation of Subutex, there was a "clear improvement" of hepatic enzymes. [ISR 3194069]
Hospitalization	20 yo male IV drug abuser with hepatitis C ALAT 50x ULN, ASAT 30x ULN, and bilirubin 200 micromol/liter. Injected heroin, cocaine, Subutex [ISR 3343189]
Elevated transaminases in hospitalized patient	89 yo woman hospitalized for treatment of postherpetic neuralgia, given carbamazepine, mianserin HCl, diclofenac, and Lepetan. Developed nausea, bradycardia, SGOT 664, SGPT 1236; medications discontinued, pacemaker inserted, "...event resolved." [MedWatch report narrative has this chronology; laboratory test data show the SGPT occurring before buprenorphine was administered. However, physician attributed elevation possibly to each of the cited medications except diclofenac.] [ISR 3995486]
Possible prolongation of hospitalization	34 yo man with HIV/HCV/HBV on buprenorphine for about 1½ yrs, then several medications including pyramethamine, sulfadiazine, and zopiclone, hospitalized for neurological event, sulfadiazine switched to clindamycin and carbamazepine added, had icterus with direct bili 45 IU/l ("4N") and AST 143/ALT 151 IU/l. Buprenorphine continued; several other medications stopped. LFTs returned to normal range [ISR 4032425]

Case qualification	Summary of case [AERS ISR number]
Hospitalization	78 yo woman who had received treatment for pain from herpes zoster. "[O]ne week and six days after last receiving Anapeine [Ropivacaine], four days after last receiving loxoprofen sodium, mecobalamin and misoprostol and four weeks and three days after last receiving buprenorphine hydrochloride" AST was 413 U/l and ALT 788 IU/l. Hospitalized for evaluation; improved. [ISR 4061918]
Hospitalization	77 yo woman with cardiac dysrhythmias and hypertensive heart disease who developed "hepatic necrosis", cardiomyopathy, and hepatorenal syndrome while taking buprenorphine, odansetron HCl, and ranitidine for unreported indications for unknown periods; took tramadol HCl for one day or less before necrosis developed. "A gradual normalization of enzymes is reported, except for pancreatic enzymes." [ISR 4108177]
Elevated transaminases in hospitalized patient	61 yo woman with history of cervical cancer operation and radiation and chemotherapy for recurrence, ilectomy for ileus, hospitalized for treatment of herpetic neuralgia. Received ropivacaine, droperidol, and buprenorphine epidurally and amitriptyline. Amitriptyline withdrawn due to increase in hepatic enzymes; 4 days later hepatic enzymes further elevated at SGOT 1309 U/l, SGPT 843 U/l, alk phos 1207 U/l. The patient was asymptomatic; medications discontinued, and the event resolved. [ISR 4208108]
Hospitalization	39 yo woman with alcoholic cirrhosis and a history of drug dependence hospitalized with edematous decompensation, hepatic encephalopathy, and refractory ascites. Had been on buprenorphine for 2 years, metoclopramide for several weeks, stopping about 2 weeks prior to the event, and spironolactone, furosemide for unreported periods. [ISR 4244307]
Hospitalization	32 yo man with drug addiction and hepatitis C on paracetamol and methadone given clonazepam about 3 weeks and Subutex and gabapentin about 2 weeks prior to presentation to emergency room with abdominal pain and elevated transaminases (ALT 19663 and AST 18145 U/l). Renal failure also diagnosed. "The events resolved on an unknown date." [ISR 4277864]
Liver failure	70 yo man with hepatitis C, cirrhosis, hepatocellular and pancreatic cancer, hospitalized for treatment of hepatocellular cancer. On teprenone, ranitidine then omeprazole; kanamycine, lactulose, and spironolactone given for unreported dates. Diclofenac was switched to buprenorphine and the next day the patient experienced hepatic encephalopathy and somnolence (ammonia increased from 69 to 129). Buprenorphine was discontinued, pentazocine was started, and two days later the outcome was reported as resolving. [ISR 4489571]
Liver failure/ death	36 yo man with HIV, Hep C, and cirrhosis, on buprenorphine for drug abuse and gabapentin for an unreported time, on Kaletra and zidovudine/lamivudine for about 9 months, hospitalized for hepatic encephalopathy a few days after starting Perinterferon and ribavirin. Kaletra and zidovudine/lamivudine were interrupted; the patient died of hepatic failure. [ISR 4550575]
Liver failure/ death	24 yo man with hepatitis C, on buprenorphine for 7 months for opioid dependence, trimipramine and levomepromazine for 3 months, and piroxicam for 2 days prior to development of "liver failure" leading to death. [ISR 4604831]
Possible prolongation of hospitalization	50 yo woman operated upon for gastric cancer, experienced increased ALT/AST on day 2, levels as high as 1000 IU/l. Buprenorphine, cefazolin, sevoflurane, fentanyl, xylocaine, diprivan, vecuronium Br, marcain, pasix, and panatol co-suspect drugs, dates of use not reported [ISR 4651887]
Liver failure	31 yo man with HIV and hepatitis C presented with jaundice and asterixis several months after starting buprenorphine as drug substitution treatment and 3 days after starting paracetamol and aspirin. ALT 6595, AST 2831; total bili 192 micromol/l, prothrombin 25%. Buprenorphine, ASA, and paracetamol stopped and clinical exam normalized; ALT and GGT reported normalized. Case reported in Berson et al., Hepatology (2001). [ISR 4759790]
Hepatic encephalopathy	40 yo man with HIV and hepatitis C, alcohol and former heroin abuse, hospitalized for pneumococcal pneumonia and pneumocystis in sputum, experienced encephalopathy and increase in bilirubin. Had been on buprenorphine as drug substitution treatment and trimethoprim/sufamethoxazole. Hyperbilirubinemia quickly decreased as burprenorphine was

Case qualification	Summary of case [AERS ISR number]
	discontinued. [ISR 4873803]
Icterus and increased transaminases	33 yo man with hepatitis C, taking buprenorphine by injection and sublingually from 1995, developed jaundice and asthenia, ALT 1330 and AST 503. Stopped injections, retained sublingual use, and jaundice disappeared, labs improved. Case reported in Berson et al., Hepatology (2001) [ISR 4936994]
Hospitalization	46 yo with HIV and hepatitis C on Subutex received amoxicillin/clavulanate for 11 days for sinusitis and was hospitalized for icterus; bilirubin was 468 micromol/l., AST 280 IU/l, and ALT 120 IU/l. Puncture biopsy showed advanced fibrosis with infiltration by neutrophils and eosinophils; MRI showed "alithiasic cholecystitis without abnormality of the ductus choledochus." He was discharged with continuous improvement. [ISR 5108146]
Hospitalization	48 yo with hepatitis C on Subutex for addiction for about 2 years, then Suboxone for about 2 months, hospitalized for "severe acute liver disease, an increased ALAT value reported as <1300 and Icterus." The tests returned to normal and the patient was rehospitalized a month later with icterus and ALAT 747, bili 81; he once again recovered. Suboxone was used throughout this period. [ISR 5402154]
Increased liver enzymes in hospitalized patient	61 yo woman with interstitial lung disease and dermatomyositis hospitalized for pneumonia, given numerous medications including voriconazole, trimethoprim/sulfamethoxazole, panipenem, minocycline, midazolam, and buprenorphine, experienced worsened liver function, possible DIC, and elevated AST 431 IU/l, ALT 265 IU/l, bili 7.1 mg/dl. Respiratory status deteriorated and the patient died. [ISR 5045942]
Possible prolongation of hospitalization	43 yo man with hepatitis C hospitalized for peritonitis that progressed to septic shock, resuscitated, received numerous medications including pethidine, doripenem, diltiazem, nicardipine, midazolam, experienced elevation of ALT to 201 and bilirubin to 6.6 mg/dl 6 days after one-day use of buprenorphine for pain relief. Lab elevations resolved with unreported action taken on medications. [ISR 5738528]
Hospitalization	64 yo man with urothelial cancer started metoclopramide some time in 2008, buprenorphine in Nov 2008, then fentanyl, escitalopram, MS Contin, Nitrazepam, dexketoprofen in early (b) (6); hospitalized for fulminant hepatitis and encephalopathy on (b) (6) Buprenorphine had been discontinued 5 days earlier. On (b) (6) "transaminases were more than 3000 (units not provided). Escitalopram, dexketoprofen, and fentanyl discontinued, ceftriaxone given, with normalization of labs and "slower recovering" encephalopathy. [ISR 6076530]

Cases reports in Table 3 did not specify whether other medications were used or whether the patient had preexisting liver disease.

Table 3. Buprenorphine severe cases in which other possible contributing causes were unknown

Case qualification	Summary of case [AERS case number]
Hospitalization	28 year-old man on buprenorphine as substitution treatment was hospitalized to analyze hepatic disorder with "transaminases up to 1500 U/l." Subutex discontinued; no mention of further course. Concomitant medications and medical history unknown. [ISR 3212927]
Hospitalization	Man of unreported age hospitalized for hemochromatosis. Had injected Subutex for unknown period of time. Concomitant medications and medical history unknown. [ISR 3344173]
Hospitalization	58 yo man on buprenorphine for an unreported period for pancreatic pain; found to have liver necrosis and no malignant process on liver biopsy. Concomitant medications and medical history unknown. [ISR 4486183]

Liver failure	60 yo man on buprenorphine for unreported indication experienced hepatic failure. Buprenorphine was discontinued, and hepatic failure resolved. Cefazolin reported as concomitant medication, but dates of use not recorded. Medical history unknown. [ISR 4589238]
Hospitalization	24 yo man on Subutex for opioid dependence experienced jaundice and dark urine and was hospitalized. "Hepatic biopsy... showed mild ductular cholestasis and isolated foci of parenchymal absterion with aspecific hepatocytic degenerative alteration. Mild portal and centro-lobular fibrosis and mild inflammatory activity were also noted. Perls coloration showed mild parenchymal haemosiderosis." Subutex was discontinued and the event resolved on an unknown date. Subsequently an increase of IgM to herpes virus was noted. Concomitant medications and medical history unknown. [ISR 4948759]

APPENDIX 2: DATABASE DESCRIPTIONS FOR DRUG USE DATA

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI: Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores,

and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Appendix 2: Tables

Table 1. Total number of dispensed prescriptions for Suboxone and Subutex by patient age (0-17, 18-25, 26-35, 36-45, 46-55, 56-65, 66+) in U.S. outpatient retail pharmacies, January 1, 2003 - December 31, 2008

2003	2004	2005	2006	2007	2008	JAN 2003 - DEC 2008 TOTAL
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(b) (4)

projected patients (ages 0-17, 18-25, 26-35, 36-45, 46-55, 56-65, 66+) who filled a prescription for Suboxone and Subutex in U.S. outpatient retail pharmacies,
 January 1, 2003 - December 31, 2008

2003		2004		2005		2006		2007		2008		JAN 2003-DEC 2008	
Projected Patient Count	Total Patient Share												
N	%	N	%	N	%	N	%	N	%	N	%	N	%



(b) (4)

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