

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-732**

**20-733**

**ADMINISTRATIVE DOCUMENTS AND  
CORRESPONDENCE**

**PATENT INFORMATION**

**Reckitt & Colman Products has no knowledge of any patent that claims the drugs or any methods of using the drugs that are the subject of this application.**

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ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 20-732/20-733 SUPPL #

Trade Name Subutex Generic Name buprenorphine HCL  
Trade Name Suboxone Generic Name buprenorphine HCL and  
naloxone

Applicant Name Reckitt Benckiser HFD- 170  
Approval Date October 8, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

NO because both applications were given an orphan drug designation and receive 7 years exclusivity.

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO /     /

b) Is it an effectiveness supplement? YES /     / NO / X /

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO /     /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

4

If it is a supplement requiring the review of clinical

data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Seven years (orphan drug)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /X/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /X/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the**

upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product (SUBUTEX)

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_X\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-401 (Buprenex)

NDA #

2. Combination product (SUBOXONE).

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_X\_/ NO /\_\_\_/

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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 18-401 (Buprenex)

NDA # 16-636 (Narcan)

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO /     /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /X/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study 1008A (N20-732)

Investigation #2, Study # Study CR96/013 (N20-733)

Investigation #3, Study # Study CR96/014 (N20-733)

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 1008A YES /\_\_\_/ NO /\_X\_/

Investigation #2 CR96/013 YES /\_\_\_/ NO /\_X\_/

Investigation #3 CR96/014 YES /\_\_\_/ NO /\_X\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Study 1008A YES /\_\_\_/ NO /\_X\_/

Investigation #2 CR96/013 YES /\_\_\_/ NO /\_X\_/

Investigation #3 CR96/014 YES /\_\_\_/ NO /\_X\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # 1008A

Investigation #\_\_, Study # CR96/013

Investigation #\_\_, Study # CR96/014

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 35,877 . YES /\_\_\_/ ! NO /\_X/ Explain:

! NIDA is the IND holder. These products are developed under Cooperative Research and Development Agreement (CRADA)

Investigation #2 !

IND # 45,219 YES /\_X\_/ ! NO /\_\_\_/ Explain:

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_

Investigation #2 !

YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_

!  
!  
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_X\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title:

Date

Signature of Office or Division Director

Date

CC:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Sara Shepherd  
10/8/02 05:31:46 PM

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Debarment Certification

Reckitt & Colman Pharmaceuticals, Inc. hereby certifies that the firm did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] in connection with this application.

Reckitt and Colman Pharmaceuticals, Inc.  
by: Alan N. Young

sig: alan N. Young

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**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-733 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number:

Stamp Date: April 8, 2002 Action Date: October 8, 2002

HFD -170 Trade and generic names/dosage form: Suboxone (buprenorphine HCL/naloxone)

Applicant: Reckitt Benckiser Therapeutic Class: type 4 / 2030401 /orphan drug

Indication(s) previously approved: NA

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: treatment of opioid dependence

**The Pediatric Rule that states "The final rule does not, however, require the submission of pediatric data for a drug for an indication or indications for which orphan designation has been granted under section 526 of Federal Food, Drug, and Cosmetic Act..."**

**Therefore this indication is exempt from pediatric studies.**

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\*

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns

Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

NDA ##-###

Page 2

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section C: Deferred Studies

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section D: Completed Studies

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/Grace Carmouze

(revised 9-24-02)

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FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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

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Sara Shepherd  
10/8/02 11:25:47 AM  
CSO

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# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-733 Supplement # \_\_\_\_\_ Circle one: SE1 SE2 SE3 SE4 SE5 SE6  
HFD-170

Trade and generic names/dosage form: Suboxone (buprenorphine/naloxone) Sublingual Tablets; 2mg/5mg; 8mg/2mg Action: AP AE NA

Applicant Reckitt & Colman Pharmaceuticals, Inc. Therapeutic Class 4PV

Indication(s) previously approved Treatment of Drug Abuse

Pediatric information in labeling of approved indication(s) is adequate \_\_\_ inadequate X

Indication in this application Treatment of Drug Abuse (For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[ /S/ ] 12-10-99  
Signature of Preparer and Title APM Date

[ /S/ ] 12-10-99  
Director/Concurrence Date

cc: Orig NDA #20-733  
HFD-170/Div File  
NDA/PLA Action Package/Kumar/Schumaker/McCormick  
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 12/10/99)

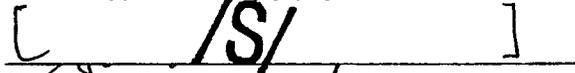
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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) [View Word Document](#)

**NDA Number:** 020733    **Trade Name:** SUBOXONE(BUPRENORPHINE HCL/NALOXONE HCL)  
**Supplement Number:** 000    **Generic Name:** BUPRENORPHINE HCL/NALOXONE HCL)  
**Supplement Type:** N    **Dosage Form:**  
**Regulatory Action:** AE    **COMIS Indication:** TREATMENT OF  
**Action Date:** 12/7/99  
**Indication # 1** Treatment of drug abuse  
**Label Adequacy:** Does Not Apply  
**Formulation Needed:** NO NEW FORMULATION is needed  
**Comments (if any):**

	<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
	0 years	16 years	Deferred	1/22/01
<b>Comments:</b> The drug substance, buprenorphine, is known to be safe in children and the injectable product is labeled for pediatric use. The indication for this product is — treatment of — Opiate addiction is rare in teenagers. However, given the experience based on the injectable formulation, it is reasonable to expect that those few patients between the ages of 16 and 18 who require maintenance therapy can be treated with the doses used in adults.				

This page was last edited on 1/24/01

  
 Signature

1-24-01  
 Date

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**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**  
**HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410**

**DIVISION DIRECTOR'S REVIEW OF NDA AND BASIS FOR ACTION**

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**NDA#** 20-732 SUBUTEX Sublingual tablets  
20-733 SUBOXONE Sublingual tablets

**Sponsor** Reckitt & Benckiser Pharmaceuticals

**Generic name** Buprenorphine HCl (SUBUTEX)  
(buprenorphine 2 mg and 8 mg tablets)

Buprenorphine HCl and naloxone (SUBOXONE)  
(buprenorphine 2 mg and naloxone 0.5 mg, and  
buprenorphine 8 mg and naloxone 2 mg)

**Pharmacologic Class:** Partial Opioid Agonist (buprenorphine)  
Opioid Antagonist (naloxone)

**Indication:** Treatment of opiate dependence

**Submissions:** Responses to Approvable letters, received April 5, 2002

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This review summarizes the basis for the approval action to be taken on the New Drug Applications for SUBOXONE, buprenorphine HCl and naloxone sublingual tablets and SUBUTEX, buprenorphine HCl sublingual tablets, for the treatment of opiate dependence.

The principal conclusions of the review team with which I concur are:

1. Buprenorphine, the drug substance, is safe and effective for
2. Buprenorphine can be delivered, using sublingual tablets, in doses that have been shown to be safe and effective.
3. Naloxone may be expected to deter intravenous abuse of buprenorphine, thus providing the justification for its inclusion in the combination drug product, SUBOXONE, as required under the fixed dose prescription drug regulation (21CFR 300.50).

A citizen's petition was received by the FDA on December 11, 2001 (Docket #OIP-0560) regarding the approval of buprenorphine sublingual tablets. Specific questions relating to the review and basis for approval were posed in the petition. These have all been thoroughly considered, and responses are contained within this review and in prior reviews generated by the Division of Anesthetic, Critical Care, and Addiction Drug Products, as well as reflected in the final approved labeling for these products

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## ***Background***

Buprenorphine is a semisynthetic thebaine-derived partial agonist of the opioid (morphine-type)  $\mu$ -receptor and an antagonist of the opioid (dynorphin-type)  $\kappa$ -receptor initially approved by the FDA (1982) in an injectable formulation, Buprenex, for the treatment of moderate to severe pain.

Since initial approval of buprenorphine, addiction researchers have explored its utility as a maintenance treatment for opiate addiction. Most of the research on buprenorphine in this clinical context was performed through NIH funding (NIDA, National Institute on Drug Abuse) through individual research grants. NIDA Medications Development Division opened IND#35,877 for the sublingual solution, and obtained a CRADA (Cooperative Research and Development Agreement) with Reckitt & Colman (now Reckitt & Benckiser), the commercial sponsor, under which IND# 45,219 for buprenorphine sublingual tablets was filed.

The development of buprenorphine in high doses as a treatment for opiate dependence began with a sublingual ethanolic solution. Indeed most of the clinical research that has been conducted with this drug substance used that formulation. The sublingual ethanolic solution of buprenorphine was

Thus, the sponsor initiated a new development program using a sublingual tablet. Since alcohol increases the bioavailability of buprenorphine, it was soon discovered that the new sublingual tablet was not bioequivalent to the sublingual solution, milligram for milligram. The ensuing development program for the tablet formulation, therefore, focused on two factors (1) establishing a relationship between the tablet and the sublingual solution which, in the absence of bioequivalence, would allow for the treating physician to accurately approximate the dosing regimen shown to be effective and safe in clinical trials using the solution and (2) absent the above relationship, adequate and well controlled studies demonstrating the efficacy of the sublingual buprenorphine tablet in the treatment of opiate addiction. In addition there has been a shift in focus to the development of a combination product with naloxone and buprenorphine which would have equivalent efficacy but would, by virtue of the small dose of naloxone present, be a deterrent to intravenous abuse.

NDA#20-732 for SUBUTEX (buprenorphine HCl) was submitted on March 28, 1997. Approvable letters were issued on June 30, 1998, January 28, 2000, and January 26, 2001. The NDA# 20-733 for SUBOXONE (buprenorphine and naloxone) was submitted on June 3, 1999. Approvable letters were issued on December 7, 1999 and January 26, 2001. The NDAs contain a single adequate and well-controlled trial of SUBOXONE vs placebo (and vs SUBUTEX), two controlled studies of the sublingual buprenorphine solution (without naloxone), and a variety of clinical pharmacology studies, pharmacokinetic studies, and small, generally investigator-initiated studies. Material is cross-referenced between NDAs.

The current NDAs are intended for maintenance treatment of opiate dependence when added to a comprehensive program of psychiatric counseling and support. Buprenorphine is thought to have some advantages over existing therapies as a partial agonist, including a purported protective effect in the setting of overdose, a ceiling effect limiting its subjective effects with increasing dose, and, with the addition of naloxone, it is hoped, a deterrent to intravenous abuse.

## ***Chemistry, Manufacturing, and Controls***

The chemical stability of the sublingual formulations of buprenorphine both as the sublingual solution and more recently as SUBUTEX and SUBOXONE was a significant factor in the protracted development time of this treatment. As noted previously, the development program for the sublingual solution was nearly complete when it was found that the solution was

Similarly, both SUBUTEX and SUBOXONE were plagued with stability problems. This was more pronounced with the new formulation, SUBOXONE due to the naloxone under normal storage

and stressed conditions. (Refer to previous memoranda and reviews). Additionally it was found that the tablets failed dissolution testing with time. In this final review cycle, dissolution testing, qualification of the impurities resulting from degradation and an assessment of the rate of degradation proved adequate. There was also adequate remedy of a newly recognized problem of — which had lead to an —  
The data provided to resolve these problems justifies an acceptable shelf life for both products.

### *Efficacy*

Substantial evidence of the efficacy of sublingual buprenorphine in the treatment of opiate addiction was provided in three adequate and well-controlled studies. These are described in detail by the primary review team and summarized by Dr. Winchell in her previous memoranda and I will discuss them briefly here.

*Study 1008* was a placebo-controlled trial in which both the SUBUTEX at a dose of 16mg/day and the SUBOXONE also at a dose of 16 mg: 4 mg/day were compared with each other and with placebo as maintenance therapy for opiate addiction. Standard and widely accepted primary endpoints for this study included (1) an assessment of abstinence by "clean" urine sampling for opiates and (2) retention in therapy (days of continuing to receive study medication from the first day in treatment). The duration of this study was only one month, and for a chronic disorder such as opiate addiction, this duration is clearly not sufficient to conclude that the product will be effective over time. Nevertheless, this study was strongly positive in support of the efficacy of both products.

*Study CR88/130* compared buprenorphine sublingual solution 8 mg (approximately comparable to 12 mg SUBOXONE) to oral methadone 20mg and 60 mg in a double-dummy, parallel-group trial with a one-week induction phase and a 4-month maintenance phase. Counseling was an integral part of treatment. Outcome measures included retention in treatment and clean urines (for nonstudy opiates). Both methadone 60 mg and buprenorphine 8 mg by sublingual route were shown to be more effective than methadone 20 mg in keeping heroin addicts in treatment and in reducing their opiate use while in treatment.

*Study CR92/099* was a 16-week dose ranging trial comparing four doses of buprenorphine sublingual solution in the treatment of opiate addiction in the setting of daily clinic visits and counseling sessions. The study compared doses of 1 mg, 4 mg, 8 mg, and 16 mg following a 1-4 day induction period. Outcome measures again included retention in treatment and clean urines (for nonstudy opiates). As in the previous study, 8 mg and 16 mg buprenorphine were shown to be superior to doses of 4 mg and 1 mg of buprenorphine, providing corroboration of the previous findings.

In part, the basis for accepting the buprenorphine SL solution efficacy data in support of the SUBOXONE application was the premise that the naloxone in SUBOXONE was not clinically effective when used as directed. It was known that there were extremely low but detectable levels of naloxone associated with the 8:2 and 16:4 doses of SUBOXONE. The application therefore had to demonstrate that these low levels of naloxone did not affect the overall efficacy of the product. In clinical pharmacology studies it was found that while naloxone in the SUBOXONE formulation when administered intramuscularly produced antagonist actions, it had no clinically significant effect when administered by the sublingual route. In addition, the efficacy of both SUBOXONE and SUBUTEX in study 1008a was established with a placebo control and the success rate for both drugs was comparable. Finally, the absence of precipitated withdrawal in patients switching from SUBUTEX to SUBOXONE (following induction) is the most compelling evidence in support of this premise.

The findings of these three clinical trials provide evidence that buprenorphine sublingual tablets at doses of 12 mg through 16 mg are effective in the treatment of opiate addiction, when administered in the context of a treatment program that includes psychiatric support and counseling. Two of these three studies were also of sufficient duration to be able to draw some conclusions about the durability of effect and about the

likelihood that some patients will demonstrate long term abstinence from illicit drugs while on safe and therapeutic doses of this medication.

The target population for this treatment is the universe of patients who suffer from opiate addiction and will include patients who in the past were only eligible for therapy with methadone and LAAM. Whether individual physicians determine which patients are more appropriate for an addiction treatment clinic-based setting to receive methadone or LAAM, or an office based setting using buprenorphine will be a matter for treating physicians to determine, and is not informed by the inclusion criteria of the efficacy studies or by the findings in these studies.

While the sponsor has developed the new formulation SUBOXONE for the maintenance treatment of opiate addiction, with the goal of reducing IV abuse, both formulations SUBUTEX and SUBOXONE have been found to be safe and effective as described above and will be marketed. Induction with SUBOXONE has not been studied in clinical trials. It is recommended that SUBUTEX will be primarily used in induction, the first few days of treatment with buprenorphine, while SUBOXONE will be the primary drug used during the maintenance phase of treatment. To avoid precipitating withdrawal, induction with SUBUTEX should be undertaken when objective and clear signs of withdrawal are evident

### *Pharmacokinetics*

The studies using the sublingual buprenorphine solution can be linked with pharmacokinetic data to buprenorphine tablets, both buprenorphine alone and buprenorphine with naloxone, to provide corroborative evidence for the safety and efficacy of buprenorphine. While the two different formulations of buprenorphine have different bioavailability, there is sufficient basis to correlate the findings in one series of studies using the more bioavailable solution with higher doses of the less bioavailable tablets.

Dr. Doddapaneni undertook an analysis that compares the dose vs. AUC plots for SUBOXONE and buprenorphine sublingual solution formulations. These curves are found to be reasonably parallel indicating that the relative bioavailability of buprenorphine as SUBOXONE compared to the solution is relatively constant across doses of 4 mg to 16 mg for SUBOXONE. The relative bioavailabilities for the doses of 4 mg, 8 mg and 16 mg were 0.72, 0.66, and 0.72. This bracketing of doses allowed for the clinical studies of the sublingual solution to be linked to the current NDA for buprenorphine/naloxone tablets. This is discussed in greater detail in the pharmacokinetics review.

Due to the transition from the liquid formulation to the tablet formulation of buprenorphine, the sponsor had developed efficacy data in a range for which there was not a corresponding tablet size. Tablets were developed in 2-mg and 8-mg doses and only two-tablet administration was studied in the efficacy and biopharmaceutical studies. The 16-mg dose that was studied and found to be effective can be administered as two 8-mg tablets. However, the lower effective dose of 12 mg, studied only in the liquid form, and an intermediate 14-mg strength, could not be dosed with only two tablets. There was a need to establish a means to administer a number of tablets at one dosing time to equal these intermediate doses. The sponsor conducted a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, comparing simultaneous dosing at various intervals, in order to provide dosing instructions to patients and physicians that will permit accurate delivery of the desired dose. The study demonstrated no significant mean differences between sequential and simultaneous dosing. However, significant interpatient variability was observed, and meaningful differences were observed when patients changed from one regimen to another. The labeling will recommend that whichever mode of administration is chosen, sequential or simultaneous, the patient be advised to adhere to that regimen permanently.

In vivo dissolution testing of the newly submitted hexagonal SUBOXONE tablets showed dissolution profiles comparable to the prior  tablets.

## **Safety**

### **Nonclinical**

The nonclinical safety was evaluated in acute, subacute and chronic studies in rats, dogs and primates. Target organ toxicity was observed only in dogs with chronic administration of up to 76-fold higher doses than the highest anticipated human dose. The toxicity that was observed was moderate bile duct hyperplasia with associated biliary fibrosis. There is a greater than 10-fold margin of safety for these findings.

While certain isolated genotoxicity studies were positive for both naloxone and buprenorphine in isolation, the genotoxicity panel was negative for the combination product. The sponsor has committed to an additional mutagenicity study to evaluate an impurity in the naloxone drug substance, which has been recently identified.

Carcinogenicity studies performed in rats demonstrated a higher incidence of testicular interstitial adenoma at 17-fold higher doses than the highest projected human dose. Carcinogenicity studies in mice were negative. The sponsor is currently undertaking a 2-year carcinogenicity study in rats using the buprenorphine/naloxone combination product.

Reproductive toxicology studies of buprenorphine and the combination of buprenorphine and naloxone were conducted. No teratogenicity was found with either buprenorphine or the combination of buprenorphine and naloxone in various ratios. As the review team points out, while none of the reproductive toxicology studies were performed using the 4:1 ratio of buprenorphine to naloxone, no interactions have been seen using higher ratios in several studies conducted in two species and two different routes of administration. Thus, they posit that it is reasonable to predict that no interactions would be present at a lower naloxone concentration. Post-implantation losses were observed in animals treated with buprenorphine and buprenorphine/naloxone in combination at doses up to 50 mg/kg administered orally.

### **Clinical Safety— buprenorphine**

Subjects participating in clinical trials of various buprenorphine formulations with CRF's include 472 exposed to SUBOXONE, 105 exposed to SUBUTEX, and 813 exposed to buprenorphine sublingual solution, for a total of 1390. These exposures were obtained in patients taking doses at or above those demonstrated to be effective for opiate addiction. Additional, less well-documented exposures have also been noted by the sponsor and adverse events of significance arising in the context of studies without CRFs, post-marketing surveillance, and published studies were also described.

In the context of the review of NDA 20-732 for SUBUTEX, the division previously concluded that there was evidence to support the safety of buprenorphine *sublingual solution* at doses up to 32 mg/day. Further examination of the buprenorphine/naloxone database as described by Dr. Winchell, who teased apart the contributions of the various components of this development plan in an earlier review, confirmed this finding.

There have been a series of isolated reports of buprenorphine-associated deaths related to hepatocellular damage, based largely on postmarketing passive reporting, but a clear attribution to buprenorphine was difficult to establish. The clinical trial data show a frequency of 12% of patients who demonstrated clinically abnormal hepatic enzymes at any point during study. In this population there is a high occurrence of confounding factors such as ongoing IV drug use, abnormal hepatic function at baseline, chronic hepatitis infection, and concurrent alcoholism that made it difficult to assign causality. Nevertheless there were some cases of patients who were seronegative for hepatitis B and C, and who had normal hepatic function at baseline who went on during buprenorphine treatment to develop clinically abnormal liver enzymes. The significance of this finding needs further exploration. The sponsor has committed to disclosing this in the package insert and to evaluating this in phase 4 in a study comparing the incidence of hepatic toxicity in patients treated with buprenorphine and methadone.

In addition to the above, Dr. Doddapaneni has identified concerns related to the metabolism and excretion of buprenorphine and naloxone in patients with hepatic failure. No studies were conducted to determine the pharmacokinetics of buprenorphine and naloxone in hepatic failure patients. Population PK indicated that the clearance of buprenorphine was decreased in patients with elevated bilirubin and ALT levels. Since naloxone is also metabolized by the liver, the increased levels in patients with hepatic failure might precipitate withdrawal. A Phase 4 commitment has been made by the sponsor to assess this further. Alternative treatment with buprenorphine alone should be considered for patients with hepatic failure until further evaluation is complete.

There were many subjects who had elevated eosinophil counts. There appeared to be a dose-dependent trend in the shift from normal to abnormally high eosinophil counts. Line listings reveal counts as high as 30 in one case, and several in the mid-20s. In many subjects, the finding was transient and resolved by the end of treatment. Eosinophilia is not unexpected in injection drug users.

Serious Adverse Events were largely related to complications of underlying disease but also included seizure, endocarditis, vomiting and diarrhea, suicidal ideation, and elevated liver enzymes. These are not unanticipated and were infrequent. Respiratory depression, despite the high doses studied in this NDA, was not a problem in these studies, as the patients enrolled in these studies were obviously opioid tolerant.

Common adverse events included headache, insomnia, constipation, anxiety, sedation, nausea, and dizziness. The clinical data in this NDA derived from clinical trial experience support the safety of sublingual buprenorphine in doses at or above 32 mg/day. The adverse events described in these studies will be described in the package insert.

The safety of SUBUTEX and SUBOXONE when abused, taken intravenously, intranasally or in conjunction with other drugs of abuse was not addressed in this application and cannot be guaranteed.

#### **Clinical Safety—Naloxone**

Naloxone in buprenorphine/naloxone is poorly absorbed sublingually, and therefore, nearly the entire dose is available for GI absorption. In the open label extension, Study 1008(b) approximately 250 patients were exposed to naloxone for up to 6 months and nearly 100 up to one year in doses for which this product will be labeled. No unexpected adverse events were noted in this experience.

#### **Clinical Safety—Abuse Liability and the Fixed-Combination Prescription Drug Regulation**

The regulation governing the approval of fixed-combination prescription drugs states that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective. It is permissible that a component be added to minimize the potential for abuse of the principal active component. In order to satisfy the requirements of the combination rule, approval under 21CFR300.50(a)(2) the naloxone component of SUBOXONE must be shown to minimize the abuse potential of the buprenorphine when intentionally self-administered intravenously. Clinical pharmacology studies were provided which demonstrated that a combination of buprenorphine and naloxone, given intravenously in a 4:1 ratio, precipitates withdrawal in subjects maintained on other opiates.

The review team has determined that the abuse of buprenorphine by the intravenous route may be reduced based on theoretical clinical grounds with the addition of naloxone, and is justified under 21CFR 300.50.

*Control of buprenorphine under the CSA (Controlled Substances Act)*

In evaluating the abuse liability of buprenorphine, the European experience in the postmarketing setting was reviewed. France has the largest experience with sublingual buprenorphine worldwide. France granted marketing authorization for buprenorphine in 1995 but the product was not marketed until 1996. At the time of launch the drug could be prescribed in the office setting but there was a network of addiction specialists who prescribed the drug in accordance with nationally recommended treatment guidelines (consultation with a specialist, psychosocial follow-up and dosage schedules). The labeling indicated buprenorphine as "substitution treatment for major opioid drug dependence, within a comprehensive therapeutic monitoring framework of medical, social, and psychological treatment".

Buprenorphine (brand name SUBUTEX) has been available in Europe in doses of 0.4 mg, 2 mg and 8 mg. A physician could write a prescription for a maximum period of 28 days.

Between its date of approval for use and late 1996, the medical service of French National Health Insurance followed 149 illicit drug users who received sublingual buprenorphine. They all lived in the Vosges region and were affiliated with French Social Security Health Insurance. In general, prescribing physicians did not follow the guidelines for treatment. Concomitant prescriptions with psychotropic drugs, mainly benzodiazepines were frequently encountered.

During this time there had been reports of fatal overdose with buprenorphine often in association with other drugs. The package insert was strengthened in 1997 to include the danger associated with "misuse" of buprenorphine.

In 1999 due to a growing problem of abuse and deaths, the French government issued more constraints on dispensation such that only a 7-day supply could be dispensed at one time per 28-day prescription. Special prescriptions were required. Buprenorphine could be obtained in boxes of 7 tablets and patients could only receive one box per week. Intravenous abuse of buprenorphine is still a problem in France. One known practice is the IV use of a portion of a prescription by patient, who sells the remainder. Theft and forgery is also reported. It should be noted that the combination product SUBOXONE is not available in France.

The presence of naloxone in the SUBOXONE formulation is likely to provide some deterrence to intravenous abuse. It is expected that if SUBOXONE is injected intravenously, the naloxone present will precipitate withdrawal or result in significant dysphoric effects. Since SUBOXONE will be the primary drug of choice for maintenance therapy, it is hoped that the US will not experience the level of abuse seen in France.

However, it is recognized that the presence of naloxone will probably not be an absolute impediment to abuse. SUBOXONE may, for example, be abused sublingually, as it has euphorogenic effects by this route, unaffected by the presence of naloxone. The extent to which intranasal abuse will be a problem remains to be seen, but there has been an increase in this alternate route of abuse in the United States, particularly among youth.

Through the course of SUBOXONE development naloxone was found to degrade under certain conditions. The sponsor supplied the NDA with information about the rate of naloxone degradation under stressed conditions. Under the conditions tested, which included \_\_\_\_\_, there was no selective degradation noted. The rate of degradation that has been shown to occur gradually with \_\_\_\_\_ was not thought to negate the value of this formulation. It has been determined that sufficient naloxone is present despite the known rate of degradation to provide antagonist effect if injected.

The FDA laboratories have additionally conducted two independent analyses to assess the ease of separability of the components of SUBOXONE. While it is of some concern that the components may lend themselves to being separated by chemical means yielding pure buprenorphine, one must also recognize that

a certain level of IV abuse in this population is probably inevitable. It is, however, expected that most IV drug abusers will not go to great lengths of performing chemical separations to obtain pure drug substance.

Buprenorphine for parenteral use has been controlled in Schedule V. The basis for this level of control was reviewed and new information considered. An Eight-Factor Analysis was conducted and a recommendation for Schedule III was developed based on new data on comparative binding at the opiate receptors, information about the product's ability to cause physical dependence, including reports of neonatal abstinence syndrome (withdrawal), and reports of actual abuse worldwide using the sublingual formulations by intranasal, sublingual and intravenous routes. Recommendation to control the drug substance buprenorphine in Schedule III of the Controlled Substances Act has been developed and was approved by the Drug Enforcement Administration (DEA)<sup>1</sup> to control buprenorphine accordingly. This new heightened schedule of control will apply to all formulations of buprenorphine, the existing parenteral formulation, Buprenex, as well as Subutex and Suboxone.

There has been considerable discussion of the advisability of allowing doses of drug for patients to take home in the United States. The FDA has received no evidence to support a general restriction of the quantities of drug allowed for take-home based on safety. Standards for take home doses are not included in the approved labeling for SUBUTEX and SUBOXONE, but rather are determined by experts in the addiction field. In addition the provisions of the Drug Abuse Treatment Act of 2000 (DATA) allow the Secretary, DHHS to impose take home restrictions only for drugs for which an "adverse determination" has been made. This has not been the case with buprenorphine. Therefore, take home doses will be allowed at the discretion of the treating physicians, all of whom will have been adequately trained.

#### ***Treatment under the DATA 2000 (Drug Abuse Treatment Act)***

The Controlled Substance Act as amended by the Section 3502 of the Children's Health Act of 2000 (P.L.106-310) provides a new mechanism for qualified physicians to dispense agonist therapy (narcotic drugs) to patients for the treatment of opiate addiction. The new statute enables qualified physicians to obtain a waiver to avoid the current requirements to dispense treatment under the Narcotic Addict Treatment Act in addiction treatment centers (methadone clinics). Each physician interested in a waiver submits a notification that certifies qualifications (medical license, regular CSA registration, adequate training and experience) and commitments (capacity to refer for services, treat no more than 30 patients) to the terms of the waiver. The Secretary must determine within 45 days whether the practitioner meets all requirements. Physicians with waivers may then prescribe Schedule III-V narcotic drugs that are approved for the treatment of narcotic addiction. The new provisions appear to intend minimal regulation and oversight, but provide the Department regulatory authority in specific areas, including credentialing bodies, practitioner education and training criteria, and limits on the number of patients to be treated by each physician.

Subutex and Suboxone will be the first narcotic drugs available under the Drug Abuse Treatment Act (DATA) of 2000 that can be prescribed in an office setting. Until recently, opiate dependence treatments in Schedule II, like methadone, could be dispensed in a very limited number of clinics that specialize in addiction treatment. As a consequence, there have not been enough addiction treatment centers to accommodate all patients desiring therapy. Under the DATA, medications that are in less restrictive controls than Schedule II can be prescribed in a doctor's office by certified physicians.

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<sup>1</sup> Federal Register/Vol. 67, No. 194/Monday, October 7, 2002/Rules and Regulations

### ***Risk Management***

Early on in the evaluation of the marketing applications for these drugs, when office-based treatment was being discussed as an option for buprenorphine, consideration was given to approval with restricted distribution (21 CFR 314.520) in an effort to reduce the potential for diversion through the addict population. In an effort to comply with the intent of the DATA, an alternative approach to the prevention of diversion and abuse was sought. The sponsor and consultants, with input from other Health and Human Services agencies including the FDA and Substance and Mental Health Services Administration (SAMHSA), and the Drug Enforcement Administration (DEA), have developed a comprehensive voluntary Risk Management Program (RMP) designed to deter abuse and diversion of these drugs from their legitimate medical setting. The two pillars of the RMP are Prevention and Surveillance. Some of the features of this program are summarized below.

### **Preventive Measures**

The RMP relies heavily on preventive measures such as education of both patients and physicians regarding proper use of these drugs, close monitoring of drug distribution channels, and child resistant packaging. In addition DATA includes limits on the number of patients allowed for each prescribing physician and requires special DEA registration for the use of buprenorphine, thus providing additional safeguards as it enters the office-based treatment setting.

One of the features of this program is that the tightly monitored distribution chain

The treatment guidelines developed and distributed by SAMHSA recommend supervised administration of induction doses. Provisions in the RMP address this. Physicians may retain supplies for supervised induction in the office if they comply with the provisions of the CSA and any relevant state law. If they choose not to do so, they are encouraged to develop a working relationship with a pharmacy that can help facilitate the process of providing initial doses on a daily basis so that induction doses can be administered by the treating physician. Physicians are encouraged to voluntarily restrict the number of take-home doses to 7 days initially.

The program provides for education for physicians, pharmacists, and patients and family. Materials such as a Physician's Brochure (FAQ's), materials provided to the American Society of Addiction Medicine, the American Psychiatric Association, and the American Academy of Addiction Psychiatry; pharmacy educational symposia and information on safeguards have been developed. There is a toll-free number and website: [www.suboxone.com](http://www.suboxone.com) which provide information regarding local controlled substances regulations.

### **Surveillance**

The RMP also provides for both traditional and non-traditional (proactive) approaches to drug abuse surveillance to identify if, and when, the drugs are being abused.

The active surveillance will include interviews with substance abusers entering treatment programs, the use of trained substance abuse street ethnographers to monitor local drug markets and drug using network areas where these products are most likely to be used and therefore abused, monitoring of media reports and websites, and a 1-800 Number for reporting theft and diversion. This active surveillance program will be coordinated by \_\_\_\_\_ This group will serve as a link to all participants, conduct training, receive and analyze data, staff a help desk to answer questions and convene Advisory Groups and provide periodic reports to the sponsor and FDA.

Some of the more traditional methods of data collection are sources of information that can indicate whether Subutex and/or Suboxone are implicated in abuse or fatalities. These include:

- DAWN—The Drug Abuse Warning Network. This is run by SAMHSA (Substance Abuse and Mental Health Services Administration), which regularly publishes a collection of data on emergency department episodes related to the use of illegal drugs or non-medical use of a legal drug.
- CEWG—Community Epidemiology Working Group. These working groups have agreed to monitor buprenorphine use.
- NIDA will also send a letter to NIDA doctors asking them to participate/be aware of the potential for abuse and to report it if necessary.

Periodic reporting of the results of these surveillance efforts will enable FDA to identify untoward effects from the availability of buprenorphine and, if indicated, to take appropriate actions to protect the public health.

### ***Risks and Benefits***

Agonist treatment for opiate addiction has been the subject of many decades of controversy. These two new products, SUBUTEX and SUBOXONE which have been shown to be safe and effective for the treatment of opiate dependence will be soon be the first drugs to be prescribed in a traditional office setting. It has not been since 1974 when previously treatments such as this were restricted to specialized and heavily regulated addiction treatment clinics. There is no question that the new statute will provide increased and needed access to treatment.

The FDA has considered the potential risks of these new products in the context of approval under the new treatment paradigm provided in the DATA. It has taken steps to increase controls on the drug substance by recommending Schedule III controls under the CSA. The FDA along with the sponsor has sought creative approaches such as the development of a comprehensive voluntary Risk Management Program with extensive provisions for training of health care personnel and surveillance for untoward effects. It considered that the DATA, while relying heavily on physician judgement to provide the best approach to serve the needs of this population, has imposed some limits on the number of patients who can be treated, and has allowed several avenues of corrective action to occur if an adverse determination is made.

A certain level of abuse in this very vulnerable population is probably inevitable. On balance, even given the experience of abuse and diversion of buprenorphine in France, the availability of the pure SUBUTEX formulation has been associated with a reduction overall in the mortality rate associated with complications of heroin addiction in France, suggesting that this treatment modality with its method of delivery may be an overall public health success. It is expected with the addition of the antagonist, naloxone, increased control of the drug substance in Schedule III, and with a proactive Risk Management Program in place at the time of approval, that SUBOXONE will have greater safeguards against abuse than its predecessor in Europe, while providing far greater access to needed addiction treatment through the new provision of the Drug Abuse Treatment Act than has been available to date.

### ***Action***

Approval of SUBOXONE and SUBUTEX for treatment of opiate addiction under the provisions of the Drug Abuse Treatment Act.

**APPEARS THIS WAY  
ON ORIGINAL**

***Phase 4 Commitments***

The following are Phase 4 Commitments have been developed in cooperation with the sponsor:

1. Perform a prospective study of the effect of buprenorphine on the liver, using a methadone-treated control group. The study should be sufficiently large and of sufficient duration to determine whether buprenorphine causes hepatic dysfunction, and to identify risk factors such as baseline viral hepatitis status, concomitant drug use, or other contributing factors.
2. Perform a study to determine the effect of hepatic impairment on the pharmacokinetics of Suboxone and Subutex, and to establish whether there is a differential effect on buprenorphine as compared to naloxone.
3. Submit adequate qualification of the potentially genotoxic drug substance impurity \_\_\_\_\_ either by demonstrating that it is a significant metabolite or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay).
4. If \_\_\_\_\_ is demonstrated to be genotoxic, or if no genotoxicity testing is submitted for it, submit adequate qualification of the other potential \_\_\_\_\_ drug substance impurities either by demonstrating that they are significant metabolites or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay).

***Pediatric Development***

pediatric studies cannot be required of a product that has received Orphan designation.

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this page is the manifestation of the electronic signature.**

/s/

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Cynthia McCormick  
10/8/02 01:53:48 PM  
MEDICAL OFFICER

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ON ORIGINAL**

3 Page(s) Withheld

## Shepherd, Sara

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**From:** O'Keeffe, Charles [Charles.O'Keeffe@reckittbenckiser.com]  
**Sent:** Tuesday, October 08, 2002 11:39 AM  
**To:** 'Shepherd, Sara'  
**Subject:** RE: Final version of PPI

Sara,

We're OK with the final changes in the package insert.

Regards,  
Charles

-----Original Message-----

**From:** Shepherd, Sara [mailto:ShepherdS@cdcr.fda.gov]  
**Sent:** Monday, October 07, 2002 3:21 PM  
**To:** Charles O'Keeffe (E-mail)  
**Cc:** Shepherd, Sara  
**Subject:** Final version of PPI

Only minor changes were made and I put them in blue.

<<Label100702.doc>>

Sara E. Stradley (formerly Shepherd)  
Regulatory Project Manager  
Division of Anesthetic, Critical Care and Addiction Drug Products  
(DACCADP)  
301-827-7430

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this page is the manifestation of the electronic signature.**  
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/s/

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Sara Shepherd  
10/8/02 07:21:43 PM  
CSO

3 Page(s) Withheld

**Shepherd, Sara**

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**From:** O'Keeffe, Charles [Charles.O'Keeffe@reckittbenckiser.com]  
**Sent:** Tuesday, October 08, 2002 12:09 PM  
**To:** 'Shepherd, Sara'  
**Subject:** RE: RMP plan was OK, correct???

Yes,

Charles

-----Original Message-----

**From:** Shepherd, Sara [mailto:ShepherdS@cdcr.fda.gov]  
**Sent:** Tuesday, October 08, 2002 11:47 AM  
**To:** Charles O'Keeffe (E-mail)  
**Subject:** RMP plan was OK, correct???

Sara E. Stradley (formerly Shepherd)  
Regulatory Project Manager  
Division of Anesthetic, Critical Care and Addiction Drug Products  
(DACCADP)  
301-827-7430

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ON ORIGINAL**

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this page is the manifestation of the electronic signature.**  
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/s/

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Sara Shepherd  
10/8/02 07:10:37 PM  
CSO

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# BEST POSSIBLE COPY RECKITT BENCKISER HEALTHCARE

Food and Drug Administration  
Center for Drug Evaluation and Research  
Anesthetic Critical Care & Addiction  
Drug Products (HFD 170)  
5600 Fishers Lane  
Rockville, MD 20857

7<sup>th</sup> October 2002

Attention: Cynthia McCormick, MD

NDA 20-732  
NDA 20-733

Dear Dr McCormick,

With reference to your fax of 2<sup>nd</sup> October 2002 detailing three Phase 4 commitments resulting from your evaluation of the NDAs for Subutex and Suboxone. We accept these Phase 4 commitments and will carry out the studies as described below to the stipulated timeline.

1. Study 1

Submit adequate qualification of the potentially genotoxic drug substance impurity \_\_\_\_\_ either by demonstrating that it is a significant metabolite or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). If \_\_\_\_\_ is determined to be genotoxic, limit it (e.g., via in-process controls or drug substance acceptance criteria) to “\_\_\_\_\_”

Protocol Submission: Within 3 months of the date of this letter  
Study Start: Within 9 months of the date of this letter  
Final Report Submission: Within 12 months of the date of this letter

If \_\_\_\_\_ is demonstrated to be genotoxic, or if no genotoxicity testing was submitted for it, submit adequate qualification of the other potential \_\_\_\_\_ drug substance impurities either by demonstrating that they are significant metabolites or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay).

If the other potential \_\_\_\_\_ drug substance impurities are determined to be genotoxic, limit the individual impurities (e.g., via in-process controls or drug substance acceptance criteria) to “\_\_\_\_\_”

Protocol Submission: Within 15 months of the date of this letter  
Study Start: Within 18 months of the date of this letter  
Final Report Submission: Within 24 months of the date of this letter

Reckitt Benckiser Healthcare (UK) Limited  
Dansom Lane, Hull HU8 7DS

TEL: (01482) 326151 FAX: (01482) 582532 Telex: 592166 RECCOL HULL

Registered in England No. 261312 Registered Office: 103 - 105 Bath Road, Slough, Berkshire SL1 3UH

2 Study 2

Submit a protocol for a prospective study of the effect of buprenorphine on the liver, using a methadone-treated control group. The study should be sufficiently large and of sufficient duration to determine whether buprenorphine causes hepatic dysfunction, and to identify risk factors such as baseline viral hepatitis status, concomitant drug use, or other contributing factors.

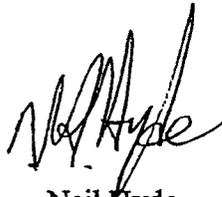
Protocol Submission: Within 6 months of the date of this letter  
Study Start: Within 12 months of the date of this letter  
Final Report Submission: Within 60 months of the date of this letter

3. Study 3

Submit a protocol for a study to determine the effect of hepatic impairment on the pharmacokinetics of Suboxone, and to establish whether there is a differential effect on buprenorphine as compared to naloxone.

Protocol Submission: Within 3 months of the date of this letter  
Study Start: Within 6 months of the date of this letter  
Final Report Submission: Within 18 month

Yours sincerely,



Neil Hyde  
Buprenorphine Development Manager  
Reckitt Benckiser Healthcare (UK) Ltd

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**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 2, 2002

<b>To:</b> Charles O' Keffe	<b>From:</b> Sara E. Shepherd
<b>Company:</b> Reckitt Benckiser	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
<b>Fax number:</b>	<b>Fax number:</b> 301-443-7068
<b>Phone number:</b>	<b>Phone number:</b> (301) 827-7430
<b>Subject:</b> Phase 4 commitments	

**Total no. of pages including cover:** 3

**Comments:** Please review and let us know if you agree with the commitments and the timing.

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**Document to be mailed:**                       YES                       NO

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Below are the phase 4 commitments. Review and let us know if the timelines and studies are acceptable. Thanks

1. Study 1

Submit adequate qualification of the potentially genotoxic drug substance impurity \_\_\_\_\_ either by demonstrating that it is a significant metabolite or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). If \_\_\_\_\_ is determined to be genotoxic, limit it (e.g., via in-process controls or drug substance acceptance criteria) to “\_\_\_\_\_”

Protocol Submission: Within 3 months of the date of this letter  
Study Start: Within 9 months of the date of this letter  
Final Report Submission: Within 12 months of the date of this letter

If \_\_\_\_\_ is demonstrated to be genotoxic, or if no genotoxicity testing was submitted for it, submit adequate qualification of the other potential \_\_\_\_\_ drug substance impurities either by demonstrating that they are significant metabolites or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay).

If the other potential \_\_\_\_\_ drug substance impurities are determined to be genotoxic, limit the individual impurities (e.g., via in-process controls or drug substance acceptance criteria) to “\_\_\_\_\_”

Protocol Submission: Within 15 months of the date of this letter  
Study Start: Within 18 months of the date of this letter  
Final Report Submission: Within 24 months of the date of this letter

2. Study 2

Submit a protocol for a prospective study of the effect of buprenorphine on the liver, using a methadone-treated control group. The study should be sufficiently large and of sufficient duration to determine whether buprenorphine causes hepatic dysfunction, and to identify risk factors such as baseline viral hepatitis status, concomitant drug use, or other contributing factors.

Protocol Submission: Within 6 months of the date of this letter  
Study Start: Within 12 months of the date of this letter  
Final Report Submission: Within 60 months of the date of this letter

3. **Study 3**

**Submit a protocol for a study to determine the effect of hepatic impairment on the pharmacokinetics of Suboxone, and to establish whether there is a differential effect on buprenorphine as compared to naloxone.**

**Protocol Submission:            Within 3 months of the date of this letter**  
**Study Start:                      Within 6 months of the date of this letter**  
**Final Report Submission:      Within 18 months of the date of this letter**

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/s/

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Sara Shepherd  
10/2/02 11:15:25 AM  
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**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**  
**HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410**

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**DIVISION DIRECTOR'S MEMORANDUM TO FILE**

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**NDA#** 20-732 SUBUTEX Sublingual tablets  
20-733 SUBOXONE Sublingual tablets

**Sponsor** Reckitt & Benckiser Pharmaceuticals

**Generic name** Buprenorphine HCl (SUBUTEX)  
(buprenorphine 2 mg and 8 mg tablets)

Buprenorphine HCl and naloxone (SUBOXONE)  
(buprenorphine 2 mg and naloxone 0.5 mg, and  
buprenorphine 8 mg and naloxone 2 mg)

**Pharmacologic Class:** Partial Opioid Agonist (buprenorphine)  
Opioid Antagonist (naloxone)

**Indication:** Treatment of opiate dependence

**Subject:** Inspection of Manufacturing Facility

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On September 25, 2002 late afternoon Terry Martin from executive operations notified me of Dr. Woodcock's request for a new manufacturing site inspection. Dr. Woodcock directed Dr. Chiu to meet with the Chemistry Review team to determine whether another inspection should take place. It was learned that the inspection approval for this review cycle was based on the Office of Compliance's practice to approve sites based on the prior "profile" of the manufacturing site rather than on an actual inspection. The last on site inspection took place in 1999. Therefore it was decided that an actual inspection would be performed during this review cycle, perhaps delaying the approval of this product beyond the October 8<sup>th</sup>, 2002 statutory deadline.

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/s/

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Cynthia McCormick  
9/27/02 01:51:21 PM  
MEDICAL OFFICER

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# Memo

**To:** Cynthia McCormick, MD  
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170

**From:** Nora Roselle, PharmD  
Safety Evaluator, Division of Medication Errors and Technical Support (DMETS)  
HFD-420

**Through:** Alina Mahmud, RPh  
Team Leader, Division of Medication Errors and Technical Support (DMETS)  
HFD-420

Jerry Phillips, RPh  
Associate Director, Office of Drug Safety  
HFD-420

**CC:** Sara E. Shepherd  
Project Manager, HFD-170

**Date:** September 12, 2002

**Re:** ODS Consult 00-0143-2; Suboxone (Buprenorphine Hydrochloride and Naloxone Hydrochloride Sublingual Tablets); NDA 20-733

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This memorandum is in response to a July 12, 2002, request from your Division for a re-review of the proprietary name, Suboxone. The proposed proprietary name, Suboxone, was found acceptable by DMETS in the initial name review on October 21, 1999 (ODS Consult 99-044). A second review was performed on May 21, 2002 and the name was found unacceptable (ODS Consult 00-0143). The following information was taken from ODS Consult 00-0143:

The Division submitted a review for the proprietary name Suboxone on August 5, 1999, which we found acceptable. Suboxone is a combination product containing the active ingredients buprenorphine hydrochloride and naloxone hydrochloride that will be indicated for opiate dependence.

However, at the time of the review DMETS was unaware of the proposal to submit a companion product namely, Subutex. Subutex contains the active ingredient buprenorphine hydrochloride. Subutex will also be indicated for opiate dependence and is presently marketed in Europe for the same indication of use.

Currently, the sponsor markets an injectable formulation of buprenorphine hydrochloride in the United States under the proprietary name Buprenex. Buprenex was approved prior to January 1, 1982 under NDA 18-401 for the treatment of moderate to severe pain. Given the existence of Buprenex, DMETS was concerned that the introduction of a different name for a new dosage form containing the same active ingredient would create confusion in the market place. DMETS recommended the best nomenclature approach to pursue was

According to e-mail from the Division, they are going to allow the use of the Subutex and Suboxone despite our original recommendations. If approved there will effectively be three products on the market from the same manufacturer that contain the same active ingredient:

Buprenex Injection (Buprenorphine Hydrochloride)  
Subutex Sublingual Tablets (Buprenorphine Hydrochloride)  
Suboxone Sublingual Tablets (Buprenorphine Hydrochloride and Naloxone Tablets)

During our final review of the name, two additional names were identified that were thought to have potential for confusion with the proposed proprietary name Suboxone. The two additional names identified by DMETS Expert Panel were Copaxone and Furoxone. After comparison of the two marketed products with the proposed product, DMETS believes that there is minimal risk for error between Suboxone, Copaxone and Furoxone.

Copaxone (Glatiramer Acetate) is used to reduce the frequency of attacks in relapsing-remitting type multiple sclerosis. Copaxone is available as a 20 mg single-use vial that needs to be reconstituted before use. The usual dose of Copaxone is 20 mg injected subcutaneously daily. Besides similar suffixes, Copaxone and Suboxone do not share similarities in dosage form (injectable vs. tablet), route of administration (subcutaneous injection vs. oral), indication for use, daily dosing, or strength (20 mg vs. 2 mg/0.5 mg, 8 mg/2 mg).

Furoxone (Furazolidone) is indicated for the treatment of bacterial or protozoal diarrhea and enteritis caused by the susceptible organisms *Giardia lamblia* and *Vibrio cholerae*. Furoxone is available as a 100 mg tablet and 50 mg/15 mL oral liquid (60 mL, 473 mL). The usual adult dose of Furoxone is 100 mg given four times a day for seven days. Furoxone and Suboxone do share similar look-alike characteristics.

*furoxone*

*suboxone*

However, besides look-alike similarities, the two drugs do not share many commonalities other than each having oral tablet dosage forms. Furoxone and Suboxone have different indications for use, dosage strengths (100 mg and 50 mg/15 mL vs. 2 mg/0.5 mg and 8 mg/2 mg), and daily doses. Due to these differences, DMETS believes that there is a low risk for confusion and error.

In conclusion, DMETS has no objections to the use of the proposed proprietary name Suboxone on the basis of sound-alike or look-alike similarities with other drug products. However, as previously stated, we believe that the safe use of this product is best managed

DMETS recommended labeling revisions to minimize potential errors; please refer to ODS Consult 99-044.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-3242.

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/s/  
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Nora L. Roselle  
9/16/02 07:53:58 AM  
CSO

Alina Mahmud  
9/16/02 08:02:55 AM  
PHARMACIST

Jerry Phillips  
9/16/02 09:04:08 AM  
DIRECTOR



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**DATE:** September 11, 2002

<b>To:</b> Charles O'Keeffe/Alan Young	<b>From:</b> Sara E. Shepherd
<b>Company:</b> Reckitt Benckiser	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
<b>Fax number:</b> 804-379-1215	<b>Fax number:</b> 301-443-7068
<b>Phone number:</b> 804-379-1090	<b>Phone number:</b> (301) 827-7430
<b>Subject:</b> NDA 20-732, NDA 20-733	

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**Total no. of pages including cover:** 18

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**Comments:** Attached is the revised DRAFT labeling. We are still working on the \_\_\_\_\_ section. Thanks, Sara Shepherd

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/s/

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Sara Shepherd  
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CSO



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**DATE:** September 11, 2002

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<b>Company:</b> Reckitt Benckiser	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
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<b>Phone number:</b> 804-379-1090	<b>Phone number:</b> (301) 827-7430
<b>Subject:</b> NDA 20-732, NDA 20-733	

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**Total no. of pages including cover:** 8

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**Comments:** Attached is the revised PPI. Thanks, Sara Shepherd

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