CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-732

20-733

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-732
NDA 20-733

Reckitt Benckiser
1909 Huguenot Road
Suite 300
Richmond, VA 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your new drug applications (NDA) dated March 28, 1997, received March 31, 1997, and June 3, 1999, received June 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Subutex (buprenorphine HCl) and Suboxone (buprenorphine HCl and naloxone HCl dihydrate) tablets, respectively.

We acknowledge receipt of your submissions for Subutex dated May 1, August 27, September 5, 11, 15, 22, 23, and 30, October 22, November 6, December 8, 11, 14, and 19, 1997; January 5, and 14, February 4, 6, and 17 (2), March 20, and 31, April 1, 6, and 14, May 5, June 10, and July 2 (2), 1998; July 28, and November 15, 1999; July 27, and 28 (2), August 8, September 6, and 26, October 19, November 14, and 29, 2000; January 8 and 31, February 7, April 3, 11, and 24, May 18, June 6, July 5, 8, 18, and 30, August 10, September 28, November 16 (2), 19, and 21, and December 3, 4, 7, 11, and 31, 2001; and January 11 and 14, February 1, 14, 19, and 25, March 5, 12, 13, 19, 28, and 30, April 4, 5, 22, 24, and 25, May 1, 2 , 6, 7, 17, and 21, June 7, 10, 17, 19, and 25, July 19 and 23, August 7, September 3, 18, 24, 25, and 27, and October 2 (2), 4, 7, and 8, 2002.

We acknowledge receipt of your submissions for Suboxone dated July 26, and 27, August 6, and 27, September 30, October 5, 6, 7, and 29, November 1, 10, 15, and 18, 1999; July 28 (2), August 8, September 6, and 26, October 30, November 14, and 29, 2000; January 8, and 31, February 7, March 28, April 3, 11, and 24, May 18, June 6, July 5, 8, 18, 25, and 30, August 10, September 28, October 12, and 30, November 6, 16 (2), 20, and 21, and December 3, 4, 7, 11, 12, and 31, 2001; and January 14, February 4, 14, 19, and 25, March 5, 12, 13, 19, 28, and 30, April 4, 5, 24, and 25, May 1, 2 (2) , 6, 7, 13, 17, 20, 21, and 22, June 7, 10, 17, 19, 25, and 28, July 8, 19, and 23, August 7, September 3, 10, 18, 19, 24, 25, 27, and 30, and October 2, 3, 4, 7, and 8, 2002.

The April 5, 2002, submissions constituted a complete response to our January 26, 2001, action letter.

These new drug applications provide for the use of Subutex and Suboxone for the treatment of opioid dependence in patients 16 years of age and older.

We have completed our review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed-upon text labeling. Accordingly, the applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling text (package insert, patient information leaflet, physician's information and information for pharmacists), and immediate container and carton labels faxed October 7, 2002. Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDA 20-732 and 20-733**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated October 7, 2002. These commitments, along with the completion dates agreed upon, are listed below.

1. Study 1
   You will submit adequate qualification of the potentially genotoxic drug substance (b)---------- either by demonstrating that it is a significant metabolite or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated (b)(4)----tested up to the limit doses for each assay). If (b)-(b)----------is determined to be genotoxic, limit it (e.g., via in-process controls or drug substance acceptance criteria) to (b)----------

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 (b)---------- is demonstrated to be genotoxic, or if no genotoxicity testing was submitted for it, submit adequate qualification of the other potential (b)--------(b)----------ither by demonstrating that they are significant metabolites or by genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated (b)(4)--- tested up to the limit doses for each assay).

If the other potential (b)----------drug substance(b)(4)------ are determined to be genotoxic, limit the individual impurities (e.g., vi----------ss controls or drug substance acceptance criteria) to "(b)------".

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
You will 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
You will 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

Submit clinical protocols to your INDs for these products. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

You have agreed to establish and maintain a risk management program including the following features:

1. Monitoring of drug distribution through wholesalers and investigation of suspicious orders

2. Distribution of educational materials to physicians, pharmacists, and patients to ensure safe and effective use of buprenorphine. The materials will use the

copy included in this letter. This educational material is labeling. Thus, any changes to the educational material must be treated the same as any other changes to the labeling for these products.

3. An active surveillance and intervention program to detect and deter abuse and diversion of Suboxone and Subutex, to include:

   a. Interviews of all individuals entering treatment at 60 geographically diverse substance abuse treatment programs representing a range of treatment modalities, and including a strong representation of programs serving adolescents, to identify product familiarity and awareness of abuse

   b. Monthly questionnaires completed by treatment facility staff

   c. Monthly surveys of private physicians concerning their awareness of illicit buprenorphine use by patients

   d. Ongoing street surveillance by a team of 10 geographically dispersed ethnographers, including 30-40 quarterly interviews per ethnographer. These interviews will focus on "street" drug users but will be broadened to included health care workers, law enforcement personnel, or other local informants in the setting of special investigations of emerging problems

   e. Media surveillance of news papers, web sites, and chat room participants

   f. Coordination with other surveillance data sources including the Community Epidemiology Working Group, the Purdue Pharma surveillance program, DAWN and TESS

   g. Provision of a toll-free number to all NIDA grantees with field workers interacting with drug abuse populations, to facilitate reporting of any abuse of Suboxone or Subutex detected in the course of their activities

   h. Establishment of an expert Advisory Group to evaluate reports and recommend interventions

   i. Quarterly reporting from your active surveillance program

   j. MedWatch reporting of adverse events detected through all aspects of the surveillance program

   k. 15-day reporting of any of the following events (in addition to those mandated by regulation):

(1) primary addiction to buprenorphine

(2) abuse of buprenorphine in opioid naive individuals

(3) death due to overdose

(4) neonatal withdrawal

You have indicated that this surveillance project will be ready for implementation before approval and will be implemented at the time of product launch and continued for at least the first five years of marketing of Subutex/Suboxone. It will be reviewed at the end of three years and an analysis of the effectiveness of this program in detecting serious trends in abuse of this product will submitted to the FDA at that time,

We remind you of your agreements in your submissions dated October 7, and 8, 2002.

1. In the event that it is determined that (b)---------- is genotoxic, you will investigate the presence of this (b)(4)---------- product in the drug product, and work with the Agency as necessary to limit its level.

2. You will perform stability testing on the first three commercial batches of each tablet strength of Subutex and Suboxone packed in HDPE bottles for the U.S. market. This is in addition to your ongoing commitment to continue the stability testing of established stability studies examining Subutex tablets and both oval and hexagonal Suboxone tablets packed in HPDE bottles.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. We expect your continued cooperation to resolve any problems that may be identified. In addition, we remind you to submit an updated analytical methods validation package following receipt of the remaining drug substance impurity reference standard and validation of the drug substance impurities method for this impurity.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Cynthia McCormick
10/8/02 06:03:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-732

20-733

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-733

Reckitt & Colman
1909 Huguenot Road
Suite 300
Richmond, VA 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your new drug application (NDA) dated June 3, 1999, received June 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suboxone (buprenorphine hydrochloride and naloxone hydrochoride) Sublingual Tablets.

We acknowledge receipt of your submissions dated July 28, August 8, September 6, September 26, November 14, and November 29, 2000, and January 8, 2001. Your submission of July 28, 2000, constituted a complete response to our December 7, 1999, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues. (NOTE: The Agency has reviewed the NDA for the original drug product manufacturing process, not the new investigational manufacturing process).

1. Concerning the tests, test methods, and acceptance criteria for the drug product:

   a. Provide an updated specification sheet, when the drug product specifications (tests, test methods, and acceptance criteria) have been agreed upon with the Agency.

   b. Update the acceptance criteria for color if the tablet is changed from light orange. In addition, identify the effect of [redacted]

   c. Provide safety qualification for individual degradation products of buprenorphine and naloxone that have acceptance criteria of [redacted]

   d. Provide acceptance criteria of not more than [redacted] for any individual unspecified degradation product of buprenorphine and of naloxone.

e. Provide identification of individual degradation products occurring at or greater (refer to ICH Q3B Guideline).

f. Provide acceptance criteria for each individual degradation product based upon the levels observed in the stability studies.

g. Provide a test and acceptance criteria (through shelf life) for individual tablet dissolution.

2. You must develop (e.g., through reformulation, more protective packaging, refrigeration storage) a more stable drug product, or alternatively provide data (see below) supporting a longer expiration dating period. The stability data provided under ICH conditions support less than a expiration dating period for the drug product. In order to support a longer expiration dating period:

a. Provide a complete characterization of the degradation product profile and safety qualification of degradation products for naloxone occurring at or greater. [NOTE: However, complete testing, tests, and acceptance criteria for individual degradation products have not been provided and the indicates individual products will occur above the qualification level of In addition, significant degradation products were noted in Subutex which have not been monitored in the stability studies for Suboxone.]

b. Provide data for individual tablet dissolution and provide data demonstrating that the use of pm for dissolution in stability studies is as sensitive and discriminating as the use of pm. [NOTE: There is a significant decrease in dissolution of buprenorphine on stability (e.g., dissolution for batch 141 after at 25°C/60% RH). Decreases in individual tablet dissolution may alter bioavailability.]

3. Identify the packaging components (DMF number, submission date, page number, and item number) used in the stability studies. Each component of the package/blister must be supported by drug product stability data. The Agency has accepted the present ICH stability studies, which used the non-child-resistant packaging (a backing is being added to this packaging to make it child-resistant), for review. However, any additional stability studies should be performed with the to-be-commercialized child-resistant packaging.

4. Provide identification for the site of packaging of the drug product batches used for the ICH stability studies and the proposed site(s) of commercial drug product packaging. Stability data must be provided for drug product batches packaged at each proposed packaging site.

5. Regarding the child-resistant packaging:

a. Provide updated labeling incorporating instructions for opening (i.e., the [redacted] the child-resistant packaging.

b. Provide data supporting the patients' [redacted] according to the proposed instructions for opening.

c. Provide confirmation that the child-resistant packaging meets the requirements of the Consumer Product Safety Commission under 16 CFR 1700.14 (a)(4) for controlled drugs.

d. Provide an updated reference (DMF number, submission date, page number, item number, composition, etc.,) for the child-resistant packaging ([redacted] to be used for the commercial drug product.

6. Conduct a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, comparing simultaneous dosing vs. sequential dosing at various intervals, in order to provide specific dosing instructions to patients and physicians that will permit the accurate delivery of the desired dose.

7. Provide a safety update, including a complete review of all existing safety data, including data from ongoing and completed studies sponsored by Reckitt & Colman's CRADA partner, NIDA, and its grantees. This update should specifically examine the potential for buprenorphine-induced hepatotoxicity, the role of viral hepatitis in increasing vulnerability to hepatotoxicity, and the proper approach to prevention and management of hepatic adverse events. Analyses should focus on outliers and extreme values, rather than measures of central tendency, and should provide comparison groups wherever available. Data sets with unique patient identifiers should be submitted together with the reports of the analyses. The analyses of uncontrolled studies of buprenorphine should compare the course seen in treated patients to the natural history of hepatic enzyme fluctuation in viral hepatitis. In addition, the safety data should be examined for any cases of acute allergic reaction to buprenorphine.

In addition, under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

a. Describe in detail any significant changes or findings in the safety profile.

b. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

(1) Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

(2) Present tabulations of the new safety data combined with he original NDA data.

(3) Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

(4) For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(5) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

(6) Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(7) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

(8) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(9) Provide English translations of current approved foreign labeling not previously submitted.

8. Develop and submit a protocol for urine screening for buprenorphine that can be made available to emergency rooms and poison control centers in order to facilitate distinguishing buprenorphine-related adverse events from events attributable to other drug use.

9. Design and submit a risk management and active surveillance program to ensure the safe and effective use of buprenorphine, and to identify trends in inappropriate use that might have adverse effects on the public health. An acceptable program must be finalized prior to approval of this application or your application for single ingredient buprenorphine sublingual tablets. The program should include the following elements:

a. Educational materials for patients and families.

b. Strategies to ensure that initial doses of the buprenorphine single-entity tablet are given under supervision as in all clinical trials supporting the application, to maximize likelihood of clinical success and to minimize risk of diversion.

c. Strategies to limit distribution of the single-entity product to induction use and use in patients for whom the combination product is not appropriate.

d. A mechanism by which pharmacies can ensure that only prescriptions from qualified physicians are filled, such as a computerized database or some alternative.

e. A program of active surveillance which would include such components as:

(1) Surveys of pharmacies to determine prescription size and number of refills.

(2) Media surveillance to include print and internet.

(2) A network of "key informants" and ethnographers to identify trends in street use of buprenorphine.

The results of such programs should be reported yearly in the annual report submitted to the NDA.

f. Regular monitoring and reporting of publicly-available passive surveillance programs/databases/surveys such as:

(1) Drug Abuse Warning Network (DAWN).

(2) Toxic Exposure Surveillance System (TESS).

(3) Drug Evaluation Network System (DENS).

(4) Community Epidemiology Working Groups (CEWG).

10. Develop and submit a common package insert for both Subutex and Suboxone.

Although not a deficiency, we note continued problems with chemical stability of naloxone (as judged by similar to the NDA stability batches) and buprenorphine dissolution (e.g., dissolution after 5 minutes for batch 208 at the beginning of the stability investigation) for the investigational batches of drug product manufactured with the manufacturing process.

Additional labeling comments will be provided when the issues identified above have been adequately addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new

indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless FDA waives or defers the requirement (63 *FR* 66632) [21 CFR 314.55 (OR 601.27)]. The Agency has not made a determination if a health benefit would be gained by studying Suboxone in pediatric patients. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations because pediatric studies should be delayed until additional safety or effectiveness data have been collected and reviewed. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specified time at which you must submit the required assessments.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Cynthia McCormick
1/26/01 02:31:13 PM

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Rockville MD 20857

NDA 20-733

DEC 0 7 1999

Reckitt and Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, Virginia 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your new drug application (NDA) dated June 3, 1999, received June 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suboxone™ (buprenorphine hydrochloride / naloxone) Sublingual Tablets, 0.5mg/2mg, 2mg/8mg.

We acknowledge receipt of your submissions dated June 3 , July 26 and 27, August 6 and 27, September 30, October 5, 6 and 7, and November 10 and 18, 1999.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following issues.

1. The identity and toxicity of the degradation products of naloxone have not been determined. Provide identification of all degradation products occurring at or above of the active ingredient, naloxone. You must follow the ICH Q3B guidance for qualification of degradation products.

2. Develop and validate analytical methods and specifications to provide a full accounting for all degradation products of naloxone. Additionally, provide a linkage between the analytical methods used by the — for generating the data at — , and the regulatory methods that are suitable for detecting and quantifying the degradation products of naloxone. Without confirmation of this determination, the — stability data may not be considered to support the expiration dating of the product.

3. Provide packaging that affords : — , and is in compliance with 16 CFR 1700.14(a)(4) for controlled drugs.

4. The stability data provided are not sufficient to assess a reasonable expiry date for the product. Information on any new packaging material should be provided. Provide

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information demonstrating compliance with USP standards, including [redacted] data. Submit a written stability protocol prior to conducting the stability studies, that includes, but is not limited to the following items:

a. [redacted] lots of the packaged product placed on accelerated, [redacted], and long-term stability testing per ICH Q1A&B guidance conditions.

b. [redacted] testing time stations; i.e., [redacted] months for accelerated and [redacted]

Provide the first [redacted] of data at time of resubmission and the additional data as they become available.

5. The stability of naloxone in this product is critical to its approval under 21CFR300.50(a)(2), in which it is stated 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. Therefore, in order to satisfy the requirements of the combination policy, the naloxone component of Suboxone must be shown to minimize the abuse potential of the buprenorphine component. If the presence and stability of naloxone cannot be assured, there is no basis for approving this product with the addition of naloxone. In order to evaluate the integrity of the unpackaged product under conditions of intentional degradation, additional testing is required. The tablets should be stressed under forced degradation conditions for sufficient time to predict the extent of degradation under abuse conditions.

6. Provide draft labeling consistent with the enclosed revised labeling. Additional changes may be made following your response to this letter.

7. Provide Phase 4 commitments for the following.

   a. Within one year of approval, evaluate the pharmacokinetics of buprenorphine and naloxone in patients with varying degrees of hepatic impairment, to determine appropriate dosage adjustment strategies.

   b.

   c.

d. Within 3 months of approval, develop a plan for postmarketing surveillance to assess the extent of abuse and diversion, the effectiveness of naloxone as a deterrent to intravenous abuse, and the extent of abuse by other routes of administration.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved. If you have any questions, call Indira Kumar, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

[/S/]

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-733
HFD-170/Div. Files
HFD-170/I. Kumar/ C Schumaker
HFD-170/McCormick/ Winchell
HFD-170/ Lee
HFD-170/Brase /Jean
HFD-170/ Maturu/D'Sa
HFD-170/Permutt
HFD-170/Klein/Calderon
HFD-870/Kim/Uppoor
HFD-102/J Jenkins
HFD-002/ORM
HFD-094/DDMS
HFD-102/ADRA
HFD-820/DNDC Division Director
HFD-40/ DDMAC (with draft labeling)
HF-35/Orphan Drugs
DISTRICT OFFICE

Drafted by: TC/November 22,1999, IK 12-6-99 3:34pm, 12-7-99 10:10am, 11:08am
Initialed by: C. Winchell 12-6-99 3:30pm, C.G. McCormick 12-7-99 9:30am, 10:50am
Final: C. Schumaker 12-6-99 2:00pm, 12-7-99 9:30am, 10:50am
Filename: 20733Suboxone AE 12-7-99

APPROVABLE (AE)