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

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