DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020732/S-006 & S-007

SUPPLEMENT APPROVAL

Reckitt Benckiser
10710 Midlothian Turnpike
Richmond, VA 23235

Attention: John Song
Manager, NA Regulatory Affairs Operations

Dear Mr. Song:

Please refer to your Supplemental New Drug Applications (sNDAs) dated November 16, 2009, received November 17, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subutex (buprenorphine HCl) sublingual tablets.

We acknowledge receipt of your amendments dated January 22, April 29, May 18, August 23, October 18, and November 3, 2010, and November 16, 2011.

These Prior Approval sNDAs propose a Risk Evaluation and Mitigation Strategy (S-006) as well as a revised package insert compliant with the Physicians Labeling Rule (S-007).

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on November 16, 2011, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 020732/S-006 and NDA 020732/S-007**." Approval of this submission by FDA is not required before the labeling is used.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

During the review of these supplemental NDAs, we have become aware of a placebo-controlled thorough QT study employing another buprenorphine containing product, Butrans, approved on June 30, 2010. The study indicated QT prolongation meeting the regulatory threshold for concern that was noted at buprenorphine plasma concentrations similar to that which could be achieved with Subutex (buprenorphine HCl) sublingual tablets. Therefore, Subutex (buprenorphine HCl) sublingual tablets may have the potential to cause QT prolongation at therapeutic doses that could result in increased risk for serious cardiac events, including life-threatening arrhythmias. Therefore, we consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of cardiac events related to Subutex (buprenorphine HCl) sublingual tablets.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of cardiac events related to your product.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1855-1. A clinical trial to assess the risk of QT prolongation with Subutex sublingual tablets, i.e., a thorough QT (tQT) trial. A comparison to methadone at typical treatment doses should be included.

It is likely this trial will need to be conducted in opioid-tolerant volunteers or new entrants to opioid dependence treatment. The timetable you submitted via email on August 6, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	January 30, 2012
Trial Completion:	December 31, 2014
Final Report Submission:	September 30, 2015

We recognize that the same postmarketing requirement for NDA 022410 Suboxone (buprenorphine and naloxone) sublingual film was issued on August 30, 2010, at the time of approval. We find it agreeable to use the same trial to fulfill the postmarketing requirement for Subutex (buprenorphine HCl) sublingual tablets.

If you plan to use the NDA 022410 Suboxone (buprenorphine and naloxone) sublingual film postmarketing requirement to fulfill this PMR, please cross-reference any relevant submissions to this NDA. Also, submit the protocol to your IND 045219 with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We

remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated August 21, 2009.

Since Subutex (buprenorphine HCl) sublingual tablet was approved on October 8, 2002, reports from your post-marketing surveillance activities have revealed an upward trend in misuse and abuse. Additionally, we have become aware of reports of children accidentally exposed to Subutex (buprenorphine HCl) sublingual tablet. Poison Control Center data revealed an increasing number of cases of accidental exposures in children aged six and younger. We consider this information to be "new safety information" as defined in section 505-1(b) of FDCA.

Pursuant to 505-1(f)(1), we have determined that Subutex (buprenorphine HCl) sublingual tablet can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of (1) exposure to Subutex (buprenorphine HCl) sublingual tablet in persons for whom it was not prescribed, including accidental exposure in children and (2) risks of abuse and misuse, listed in the labeling. The elements to assure safe use will inform patients of the serious risks associated with Subutex (buprenorphine HCl) sublingual tablet and the appropriate conditions of safe use and storage of Subutex (buprenorphine HCl) sublingual tablet. The elements to assure safe use will also ensure adequate clinical monitoring of patients by the healthcare providers.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on November 16, 2011, and appended to this letter, is approved.

The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of Subutex sublingual tablets
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
4. A survey of healthcare providers' understanding of the serious risks of Subutex sublingual tablets and the:
    a. need for appropriate patient monitoring
    b. need for patient adherence to conditions of safe use
    c. need to check that patients are using the drug appropriately and making adequate progress towards treatment goals
    d. need to make sure prescriptions are provided in amounts commensurate with patient stability
    e. importance of psychosocial support services

    Stratify the results of the healthcare providers' survey by stage of treatment (i.e., new entrants [month 1] vs. established patients [month 2+]). In particular, apply this stratification to the analysis of the 12 possible steps healthcare providers use to reduce inappropriate use or diversion in their practices.
5. Specific measures that will be taken to increase awareness if surveys of prescribers indicate that prescriber awareness is not adequate
6. An analysis to evaluate Subutex sublingual tablets utilization patterns including frequency of office visits, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important to safe use

    Stratify the analysis of utilization patterns (frequency of office visits per patient, amount of medication dispensed in prescriptions, etc.) by stage of treatment (i.e., new entrants [month 1] vs. established patients [month 2+])
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance will include, among other sources, reports from street ethnography programs and pediatric exposures
8. Requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
9. Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With

respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020732 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020732
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020732
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory

comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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 Matt Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

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

/s/

JUDITH A RACOOSIN
12/22/2011