DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021306/S-015
NDA 021306/S-019

SUPPLEMENT APPROVAL

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Executive Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your Supplemental New Drug Applications (sNDA) submitted January 25, 2013, (S015) and January 21, 2014, (S019) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Butrans (buprenorphine) Transdermal System.

We acknowledge receipt of your amendments dated August 7, and October 11, 2013, and April 29, 2014, (S015) and February 24, March 5, April 30, and June 24, 2014 (S019).

These "Prior Approval" supplemental new drug applications propose the following:

S015	Addition of carton and container "flags" to ensure that strengths over 5 mcg/hour are used only in opioid-experienced patients.
S019	7.5 mcg/hour intermediate dosage strength of Butrans (buprenorphine), and a proposed modification to the approved REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is 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 that includes labeling changes 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 immediate container labels that are identical to the enclosed carton and immediate container labels 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 *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 **Final Printed Carton and Container Labels for approved NDA 021306/S-015** and "**Final Printed Carton and Container Labels for approved NDA 021306/S-019**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Butrans (buprenorphine) was originally approved on June 30, 2010, and REMS modifications were approved on July 9, 2012, April 15, 2013, and July 25, 2013. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modification to the ER/LA Opioid Analgesic REMS consists of the addition of the 7.5 mcg/hour intermediate dosage strength to the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics.

Your proposed modified REMS, submitted on June 24, 2014, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 9, 2012. There are no changes to the REMS assessment plan described in our July 9, 2012, letter.

This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments. This single, shared system, known as the Extended-release/Long-acting (ER/LA) Opioid Analgesic REMS Program, currently includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 021306 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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.

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 021306 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021306
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021306
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

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, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Appendix 1: List of applications having the
ER/LA opioid analgesics REMS
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/

RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT
06/30/2014