DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788/S-009
NDA 202788/S-011
NDA 202788/S-012

SUPPLEMENT APPROVAL

Insys Therapeutics, Inc.
1333 South Spectrum Blvd., Suite 100
Chandler, AZ 85286

Attention: Stephen Sherman
Vice President, Regulatory Affairs

Dear Mr. Sherman:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received February 25, 2013, (S-009), December 19, 2013, (S-011), and May 20, 2014 (S-012) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subsys (fentanyl sublingual spray).

We also acknowledge receipt of your amendments dated September 12, 2013, and February 13, March 11, and July 23, 2014, for S-009; February 20 and 26, and April 29, 2014, for S-011; and November 26, and December 11, 2014 for Supplement S-012. Finally, we refer to the May 20, November 25, and December 10, 2014, submissions to DMF (b) (4), which contain the proposed modifications to your shared risk evaluation and mitigation strategy (REMS) program.

S-009 is a "Prior Approval" supplemental new drug application which proposes revisions to the DOSAGE AND ADMINISTRATION, HOW SUPPLIED/STORAGE AND HANDLING, and PATIENT COUNSELING INFORMATION sections of the package insert, as well as to the Medication Guide, to provide for an alternate system for Subsys disposal.

S-011 is a "Changes Being Effected" supplemental new drug application which provides for a new secondary packaging facility as well as a reduction in the size of the blister packages.

S-012 is a "Prior Approval" supplemental new drug application which proposes modifications to the approved REMS for Subsys which is part of the single shared system REMS, the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access Program.

APPROVAL & LABELING

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 and with the minor editorial revision listed below:

Revise the following line on the blister package labeling for the 1600 mcg dosage strength:

Use two sprays (one spray from each device) to achieve a total of (b) (4) mcg.

This line should be revised to read:

Use two sprays (one spray from each device) to achieve a total of 1600 mcg.

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 immediate container labels submitted on April 29, 2014, except with the revision listed above, 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 202788/S-011**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product 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 TIRF Products, of which Subsys is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on November 7, 2013. Subsys was approved and incorporated into the shared system REMS as result of approval on January 4, 2012. 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.

Your proposed modifications to the REMS consist of revisions to the Medication Guide (MG) for Subsys to include instructions for use of the new disposal system.

In addition, your proposed modifications to the TIRF REMS, including appended REMS materials as applicable, consist of the following:

1. Removal of NDC Numbers from the following:
    i. Independent Outpatient Pharmacy Enrollment Form
    ii. Chain Outpatient Pharmacy Enrollment Form
    iii. TIRF REMS Website
2. Removal of reference to generic equivalents of specific products and replacement with a footnote in the following:
    i. Education Program for Prescribers and Pharmacists
    ii. TIRF REMS Website

3. Removal of “Attachment 1: List of TIRF Medicines Available Only through the TIRF REMS Access Program," and replacement with a hyperlink to the new TIRF REMS Webpage in the following:
    i. TIRF REMS Document
    ii. Overview for Prescribers
    iii. Prescriber Enrollment Form
    iv. Overview for Patients and Caregivers
    v. Independent Outpatient Pharmacy Overview
    vi. Chain Outpatient Pharmacy Overview
    vii. Closed System Outpatient Pharmacy Overview
    viii. Independent Outpatient Pharmacy Enrollment Form
    ix. Chain Outpatient Pharmacy Enrollment Form
    x. Closed System Outpatient Enrollment Form
    xi. Inpatient Pharmacy Enrollment Form
    xii. Distributor Enrollment Form
    xiii. TIRF REMS Website and Website Landing Page
4. Revised criteria for inactivation of Patient-Prescriber Agreement Form (PPAF) in the TIRF REMS Document
5. Revisions to enhance knowledge about conversion of TIRF Medicines in the following:
    i. Education Program for Prescribers and Pharmacists
    ii. TIRF REMS Website
6. Information clarifying the process to electronically transmit TIRF REMS Cash Claims in the following:
    i. TIRF REMS Document
    ii. TIRF REMS Access Program Frequently Asked Questions (FAQ)
    iii. Independent Outpatient Pharmacy Overview
    iv. Chain Outpatient Pharmacy Overview
    v. Closed System Outpatient Pharmacy Overview

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 modified REMS, submitted on May 21, 2014, and amended on December 11, 2014, and appended to this letter, is approved.

The TIRF REMS Access Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM309784.pdf
Other products may be added to the TIRF REMS Access Program in the future if additional TIRF NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 5, 2012. There are no changes to the revised REMS Assessment Plan attached to our August 21, 2014, REMS Assessment Acknowledgment/REMS Assessment Plan Revisions letter.

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. Also, under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

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 202788 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.

Prominently identify any 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 202788
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 202788
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 202788
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 Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
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/

SHARON H HERTZ
12/24/2014