

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

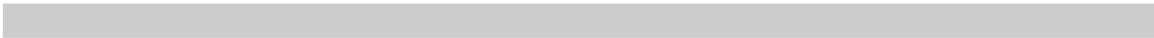
Application Information		
NDA # 202788	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Subsys Established/Proper Name: fentanyl Dosage Form: sublingual spray Strengths: 100, 200, 400, 600, 800 mcg		
Applicant: Insys Therapeutics		
Date of Receipt: March 4, 2011		
PDUFA Goal Date: January 4, 2012		Action Goal Date (if different): Possibly mid-December
Proposed Indication(s): Management of breakthrough cancer pain in opioid tolerant patients with malignancies		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Actiq (NDA 020747)	Nonclinical labeling

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

BA/BE studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Actiq	020747	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

NDA# 019813 Duragesic

NDA# 020747 Actiq

NDA# 022266 Onsolis

NDA# 022510 Abstral

NDA# 021947 Fentora

NDA# 016619 Sublimaze

NDA# 021338 Ionsys

NDA # 022569 Lazanda

various refer to Orange book for fentanyl
ANDAs complete list

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Cleared on 1/3/11
S. Stradley

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/s/

SARA E STRADLEY
01/04/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September, 7 2011

From: LCDR Alan Stevens, Infusion Pump Team Leader WO66, RM 2561
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Kathleen Davies, Project Manager, WO22 RM3189
CDER/OND/ODEII/DAAAP

Subject: CDRH Consult, GEN 1100679, NDA 202788, sublingual spray unit dose system to deliver Fentanyl

1. Issue

The Center for Drug Evaluation and Research (CDER)] has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 202788. The device constituent of this combination product consists of a sublingual spray unit dose system.

2. Device Description



(b) (4)

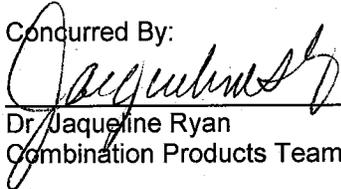
no further mitigations are required. However, no design controls are identified. Instead, the dFMEA has identified manufacturing controls. Please modify the dFMEA to identify design controls and provide evidence that implementation of the design controls are effective.

If you have any questions, please contact LCDR Alan Stevens at 301-796-6294.

Sincerely,

LCDR Alan Stevens
Mechanical Engineer

Concurred By:



Dr. Jacqueline Ryan
Combination Products Team Leader

The Fentanyl Sublingual Spray unit dose system consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder. (b) (4)

(b) (4)

(b) (4)

3. Documents Reviewed

NDA 202788, Sequence 0000, Section 3.2.P.7 (Container Closure System)
NDA 202778, Sequence 0000, Section 3.2.P.2 (Design Failure Modes and Effects Analysis)
Drug Master File (b) (4) – (b) (4)

4. CDRH Review and Comments

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of the Failure Modes and Effects Analysis.

Design Failure Modes and Effects Analysis

The dFMEA analyzed failure modes associated with each component of the device constituent, including:

- Container (glass vial)
- Plunger (stopper)
- Cannula (needle)
- Insert (nozzle)
- Container holder (vial holder)
- Actuator
- Spray Pin

For each component, the sponsor identifies potential failure modes and associated causes.

The sponsor claims to have identified design controls for each failure mode and, based on their analysis, concludes that no further mitigations are required. However, no design controls are identified. Instead, the sponsor has identified manufacturing controls.

The sponsor should identify design controls for each failure mode, and provide data verifying the effectiveness of each control measure.

DMF (b) (4) contained only biocompatibility test reports for materials of construction, which were not reviewed at this time.

5. CDRH Recommendation

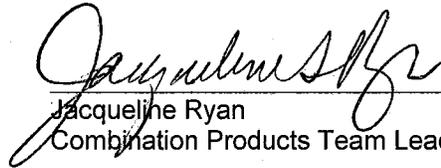
Based on our review, the following deficiencies should be conveyed to the Sponsor:

1. You have provided a design failure modes and effects analysis. For each component, you have identified potential failure modes and associated causes. You claim to have identified design controls for each failure mode and, based on the analysis, conclude that

ADDENDUM:

December 28, 2011

I have reviewed the dFMEA provided by the sponsor. It appears comprehensive. The device is quite simple, and all of the risk priority numbers fell within an acceptable range. The most common failures result in under dosing or no doses. All of the failures have a severity rating of 3 or less, which is entirely acceptable. I regard this device issue as resolved.


Jacqueline Ryan
Combination Products Team Leader


Richard Chapman
Branch Chief, GHDB

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/s/

SARA E STRADLEY

12/28/2011

Dec 28, 2011 amended consult review from CDRH.



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 21, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **NDA 202788 Fentanyl Sublingual Spray**
Indication: Breakthrough cancer pain
Dosages: 100, 200, 400, 600 or 800 µg of fentanyl per (b) (4) spray
Sponsor: Insys Therapeutics

Materials reviewed: Previous NDA review by Chad J. Reissig, Ph.D.
Chemistry Review by Julia C. Pinto, Ph.D.
Previous IND review (72,411) by Jovita Randall-Thompson, Ph.D.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested clarification from the Controlled Substance Staff (CSS) regarding the following recommendation provided in the CSS review, dated November 30, 2011:

Improve the FSS device to avoid accidental disassembly by caregivers, children, and pets (e.g. chewing or crushing), and to prevent misuse.

Initial concerns of this reviewer were based on personal observation of how easily the FSS sample device provided by the Sponsor could be disassembled, thus presenting a potential accidental exposure risk to children and pets. However, based upon the conclusions stated in the final Chemistry review (DARRTS, NDA 202-788, Julia C. Pinto, November 21, 2011), that the product attributes are adequate and the device meets CMC requirements, I retract my prior recommendation. Thus, the Sponsor does not need to improve the construction of the FSS device.

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/s/

CHAD REISSIG
12/21/2011

SILVIA N CALDERON
12/21/2011

MICHAEL KLEIN
12/21/2011



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September 14, 2011

From: LCDR Alan Stevens, Infusion Pump Team Leader WO66, RM 2561
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Kathleen Davies, Project Manager, WO22 RM3189
CDER/OND/ODEII/DAAAP

Subject: CDRH Consult, GEN 1100679, NDA 202788, sublingual spray unit dose system to deliver Fentanyl

1. **Issue**

The Center for Drug Evaluation and Research (CDER)] has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 202788. The device constituent of this combination product consists of a sublingual spray unit dose system.

2. **Device Description**



The Fentanyl Sublingual Spray unit dose system consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder. (b) (4)

(b) (4)

3. Documents Reviewed

NDA 202788, Sequence 0000, Section 3.2.P.7 (Container Closure System)
NDA 202778, Sequence 0000, Section 3.2.P.2 (Design Failure Modes and Effects Analysis)
Drug Master File (b) (4)

4. CDRH Review and Comments

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of the Failure Modes and Effects Analysis.

Design Failure Modes and Effects Analysis

The dFMEA analyzed failure modes associated with each component of the device constituent, including:

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- Spray Pin

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The sponsor claims to have identified design controls for each failure mode and, based on their analysis, concludes that no further mitigations are required. However, no design controls are identified. Instead, the sponsor has identified manufacturing controls.

The sponsor should identify design controls for each failure mode, and provide data verifying the effectiveness of each control measure.

DMF (b) (4) contained only biocompatibility test reports for materials of construction, which were not reviewed at this time.

5. CDRH Recommendation

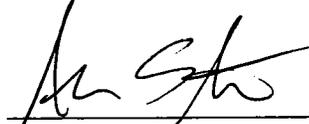
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no further mitigations are required. However, no design controls are identified. Instead, the dFMEA has identified manufacturing controls. Please modify the dFMEA to identify design controls and provide evidence that implementation of the design controls are effective.

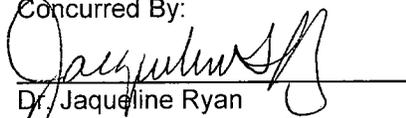
If you have any questions, please contact LCDR Alan Stevens at 301-796-6294.

Sincerely,



LCDR Alan Stevens
Mechanical Engineer

Concurred By:



Dr. Jacqueline Ryan
Combination Products Team Leader

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/s/

SARA E STRADLEY

12/15/2011

Submitting this review to DARRTS for CDRH.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 8, 2011

To: Kathleen Davies, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee' Toombs, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

CC: Shefali Doshi, Group Leader, DDTCP, OPDP
Mathilda Fienkeng, Regulatory Review Officer, Division of Professional Promotion (DPP)
Olga Salis, Senior Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 202788
DDTCP labeling comments for SUBSYS (fentanyl) Sublingual Spray, CII Medication Guide

DDDTCP has reviewed the Medication Guide (Med Guide) for SUBSYS (fentanyl) Sublingual Spray - CII (Subsys) which was submitted for consult on March 30, 2011. DDMAC used DMPP's tracked changes version of the Med Guide as the base document for review. DMPP's review of the Med Guide is being provided to the Reviewing Division under separate cover. We conferred with DMPP to the extent possible for consistency in our comments.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
12/08/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: December 8, 2011

To: Bob A. Rappaport, MD, Director
**Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): SUBSYS (fentanyl) CII

Dosage Form and Route: sublingual spray

Application Type/Number: NDA 202-788

Applicant: Insys Therapeutics, Inc

OSE RCM #: 2011-1030

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for Subsys (fentanyl) sublingual spray.

The purpose of the Applicant's submission is to seek approval of their original New Drug Application (NDA) 202-788 for Subsys (fentanyl) sublingual spray. The proposed indication is for the management of breakthrough cancer pain in patients (b) (4) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Subsys (fentanyl) sublingual spray is a member of the Transmucosal Immediate Release Fentanyl (TIRF) class of opioid products, and if approved, will be part of the TIRF REMS Access program, shared REMS for the TIRF class. The REMS is being reviewed by DRISK and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft SUBSYS (fentanyl) sublingual spray Medication Guide (MG) received on March 4, 2011, revised by the Applicant on June 29, 2011 in response to a Filing Communication dated May 11, 2011, further revised by the Applicant during this review cycle and provided to DMPP by DAAAP on November 17, 2011.
- Draft SUBSYS (fentanyl) sublingual spray Prescribing Information (PI) received March 4, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on November 17, 2011.
- Approved Abstral (fentanyl) sublingual tablet (NDA 22-510) comparator labeling dated January 7, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable, and other MGs within the TIRF class
- The enclosed IFU review comments are collaborative DMPP and DMEPA comments.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
12/08/2011

BARBARA A FULLER
12/08/2011

LASHAWN M GRIFFITHS
12/08/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 30, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

Subject: **NDA 202788 Fentanyl Sublingual Spray**
Indication: Breakthrough cancer pain
Dosages: 100, 200, 400, 600 or 800 µg of fentanyl per (b) (4) spray
Sponsor: Insys Therapeutics

Materials reviewed: NDA 202788 located at: \\ \CDSESUB1\EVSPROD\NDA202788
Previous IND review (72,411) by Jovita Randall-Thompson, Ph.D.
Peer-reviewed journals (see: references)

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I. Summary

A. Background

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Controlled Substance Staff (CSS) to review the abuse-related safety risks of fentanyl sublingual spray (FSS). Insys Therapeutics filed the current New Drug Application (NDA) for FSS through the 505(b)(2) approval pathway.

Fentanyl (Schedule II) has a known abuse potential that has been demonstrated in preclinical (Broadbear et al. 2004) and clinical abuse potential assessments (Baylon et al. 2000). The pharmacological and analgesic effects of fentanyl are mediated primarily through mu-opioid receptors. FSS is a new formulation of fentanyl intended for the treatment of breakthrough cancer pain in opioid-tolerant patients. FSS contains the same drug substance (i.e., fentanyl) as other fentanyl formulations including oral, injectable, and transdermal products.

FSS will be marketed in single use, single dose, disposable units of 100, 200, 400, 600, and 800 µg. Each individual unit will contain (b) (4) of fentanyl solution and dispense (b) (4) when used (actuated).

Across four studies examining the pharmacokinetics of FSS, the T_{max} ranged from 0.50-1.28 hours (30-117 min). FSS reached peak plasma levels less rapidly than fentanyl injection (T_{max} 0.16 h or 9 min) but faster than ACTIQ (T_{max} 1.7 h or 102 min.). The C_{max} varied as a function of dose, with the 400 µg dose of FSS reaching a C_{max} that is less than 100 µg of IV fentanyl.

FSS will be packaged in three different configurations containing 6, 14, or 28 devices in a carton. Each carton will come with a disposal system to accommodate both used and unused devices. The FSS disposal system consists of a plastic container containing (b) (4) a sealable pouch. The (b) (4) container is used for the collection and disposal of fentanyl solution from unused FSS units; the pouch is designed for the disposal of used/discharged FSS units. The results of extraction studies of fentanyl from used devices and the (b) (4) disposal system are discussed within the body of this review (see: CHEMISTRY section).

B. Conclusions:

1. Fentanyl sublingual spray (FSS) contains fentanyl, a potent, Schedule II, µ-opioid agonist with a high abuse potential.
2. The FSS system appears to have a potential for abuse, misuse, and addiction that is similar to existing fentanyl products, and a fast onset.
3. The major risk associated with FSS is accidental exposure and dosing of children, pets, and unsuspecting individuals. The benign, non-harmful appearance of FSS presents a risk of mishandling, and improper disposal, and increases the risk of accidental exposure.
4. If properly implemented, the (b) (4) disposal system is adequate.
5. Motivated individuals may disassemble or manipulate the FSS device for the purpose of injecting the internal fentanyl solution.

C. Recommendations:

(To be conveyed to the Sponsor)

1. Add a prominent warning label to the FSS device to reduce accidental exposure, improper handling, and ensure proper disposal.
2. Improve the FSS device to avoid accidental disassembly by caregivers, children, and pets (e.g. chewing or crushing), and to prevent misuse.

II. Discussion

A. Chemistry

1. Product information

The FSS system consists of a clear, colorless solution inside the FSS device. Each (b) (4) of fentanyl solution contains the following ingredients: dehydrated alcohol (b) (4), propylene glycol (b) (4), L-menthol (b) (4), xylitol (b) (4), and purified water (b) (4). The device consists of an actuator, insert, spray pin, needle, stopper, glass vial, and a vial holder (fig. 1). According to the Sponsor, FSS has undergone extensive testing to confirm the stated dose delivery and mechanical operation of the device, including tests of droplet size, spray pattern, and plume geometry. Spray content uniformity and droplet size have also been tested when actuating the device in a horizontal orientation (e.g. for the use of FSS by bed-ridden patients in the supine position). According to the Sponsor, the device operates properly in both the vertical and horizontal positions.

Residual drug in used devices (post-actuation)

Because fentanyl is a very potent opioid, the amount of residual drug remaining in the device after use is a significant concern. According to the Sponsor, approximately (b) (4) of drug solution remains in each device after use. The Sponsor contends that (b) (4), limiting its accessibility.

Based on a “worst case”, theoretical scenario, at the maximum dose of FSS (800 µg/ (b) (4) (b) (4) of fentanyl would remain in an actuated/used device. The maximum carton size contains 28 devices. Extraction of all the residual fentanyl from the maximum dose of FSS at the maximum carton size would yield (b) (4) (28* (b) (4)), or (b) (4) mg of fentanyl.

The Sponsor conducted a study (Study CHP10010) to determine the amount of fentanyl that could be recovered from used FSS devices, using simple experimental procedures with commonly available utensils that do not require expertise in chemistry. The conditions included:

- Crushing the vial wrapped in a cloth then orally absorbing the residual fentanyl by placing the cloth in the mouth.
- Using a nail, screw, paperclip, or needle to remove the stopper, then chewing the stopper.
- Using a syringe to extract residual medication from the vial for the purpose of obtaining fentanyl for injection.

- Heating the device using common kitchen appliances (a microwave, pot of boiling water, and oven) to disassemble the sprayer and access to the medication.
- Using a flame from a lighter or candle to inhale medication from a disassembled sprayer.
- Applying suction on the nozzle by sucking on the device.

The most efficient and effective method for retrieving fentanyl was via a syringe. Using a syringe, a maximum of 42.7% of the residual fentanyl was recovered (about (b) (4) device at the maximum FSS dose).

Studies examining the removal of the fentanyl solution from unused FSS units were not performed, but are not necessary as the fentanyl substance is readily abusable in intact form.

FSS housing unit disposal system (pouch)

For disposal of used FSS devices, patients are instructed to use a sealable pouch that is disposed in the trash. The pouch can be re-opened with relative ease after closing. The unlabeled pouch may provide minimal prevention of the retrieval of used devices from refuse containers (i.e. the trash) by masking the appearance or hiding the product. However, the pouch itself does not prevent physical access to used FSS devices.

Unused FSS solution disposal system ((b) (4) based bottle)

For disposal of the fentanyl solution within unused FSS devices, the Sponsor has developed a (b) (4) based disposal system. The system consists of a 100 cc plastic (HDPE) bottle (b) (4). Patients are instructed to actuate devices inside the bottle for disposal of the fentanyl solution. The used/actuated FSS device is then placed in the sealable pouch for disposal in the trash (see above).

Fentanyl disposal bottle ((b) (4) based bottle) extraction studies

The Sponsor has conducted extraction studies to examine the amount of fentanyl that can be retrieved from the (b) (4) based disposal system. In the fentanyl recovery from (b) (4) study (study CHP11001), (b) (4) were weighed into a bottle, and 28 FSS devices of the maximum dose (800 µg) were actuated into the bottle. In total, (b) (4) of fentanyl were deposited into the bottle. This represents the “worst case” scenario, where the maximum dose and maximum carton size of FSS would require disposal.

Eight separate extraction studies were performed using different extraction techniques including:

1. Overnight alcohol heating extraction

2. Overnight water heating extraction
3. Water extraction
4. Alcohol extraction
5. Alcohol heating extraction
6. Water heating extraction.
7. Consumable ethanol extraction study (i.e. Bacardi Rum)
8. Isopropyl alcohol extraction

The isopropyl extraction study (experiment #8) yielded the greatest percentage of fentanyl recovery. The cumulative amount of fentanyl recovered (after two sequential extractions) was (b) (4) or 5.94%.

In a separate study (study CHP11014), additional extraction studies were performed using various organic and inorganic solvents at different temperatures. Similar to the previously described extraction study, (b) (4) were weighed into a bottle, and 28 FSS devices of the maximum dose (800 µg) were actuated into the bottle. In total, (b) (4) mg of fentanyl were deposited into the disposal bottle.

Extraction studies were then performed using different extraction techniques. In each experiment, fentanyl recovery was measured at four time points (after 1, 3, 6, and 12 hours). Multiple experimental manipulations were performed using several solvents combined with agitation, and at variable temperatures ranging from room temperature to 90 °C depending on the solvent. Several extraction mediums were used including:

1. Dehydrated alcohol, isopropanol, and ethyl acetate
 - a. At room temperature with agitation
 - b. Heated to 70°C with agitation
2. Acetone and methanol
 - a. At room temperature with agitation
 - b. Heated to 50°C with agitation
3. Water, 6N HCl, and 6N NaOH
 - a. At room temperature with agitation
 - b. Heated to 90°C with agitation

The best single point extraction condition was achieved with dehydrated alcohol at room temperature for 1 hour. This condition afforded (b) (4) mg of fentanyl (1.23%). When examining serial extractions (e.g., the cumulative result of repeated extraction attempts) the most efficient extraction method was achieved with isopropanol at room temperature over a course of 12 hours. Using this method, (b) (4) mg of fentanyl was recovered (1.6% of the (b) (4) mg present in the disposal bottle).

Overall, the (b) (4) based disposal system appears adequate.

2. Products with potential tamper resistance claims

The Sponsor has not made specific tamper resistant claims. This formulation has a high potential for abuse through the intended route, Each FSS unit contains a liquid fentanyl solution that is readily injectable. The Sponsor claims that [REDACTED] (b) (4)

[REDACTED] However, in this reviewer's hands, FSS sample units were relatively easy to disassemble. Because the rubber stopper portion of the unit is designed to be "pierced" by a needle, it appears as though it would be easy to draw fentanyl solution into a needle for the purpose of injection.

Childproof packaging

Each individual FSS unit will be enclosed in a blister package. The blister package was evaluated for child-resistance properties. In a test of 50 children (n=50), aged 42-51 months, the FSS package was found to be 98% child resistant (study # 1759-003).

Disposal

See above (1. "product information")

Pharmacokinetics / pharmacodynamics parameters of parent drug & active metabolites

FSS provides a unique pharmacokinetic profile that involves an initial, rapid rise in blood plasma levels, and a slower, more continuous absorption of fentanyl from the GI tract. Thus, the pharmacokinetics of FSS vary depending on the proportion of swallowed versus buccally absorbed fentanyl.

Across four studies, the T_{max} of FSS ranged from 0.50-1.28 hours (30-117 min). This onset was slower than fentanyl injection (T_{max} 0.16 h or 9 min) but faster than ACTIQ (1.7 h or 102 min.). The C_{max} varied as a function of dose, with the 400 µg dose of FSS being slightly less than 100 µg of IV fentanyl.

B. Clinical Studies

1. Evidence of misuse and diversion in clinical trials

A total of six clinical studies were performed with FSS. Few abuse-related AEs were observed. However, the pivotal clinical trials involved opioid-tolerant cancer patients that may be less susceptible to abuse and abuse related AEs, and take a variety of concomitant medications.

In study FNY-P4-270, healthy subjects (n=9) were enrolled in a single dose, single blind, ascending dose trial to determine the pharmacokinetics, safety, and tolerability of FSS under fasting conditions. FSS doses of 100, 400 and 800 µg were administered. A total of 131 AEs were observed across the nine volunteers. Few abuse-related AEs were observed, although all were observed at a higher incidence than placebo. AEs included "feeling drunk", "feeling of relaxation", "disturbance in attention", and "somnolence".

Study INS-06-003 compared the absorption rate of FSS to reference fentanyl products. Healthy subjects (n=40) received 400 µg FSS. No abuse-related AEs were observed by any study participants receiving FSS.

Study INS-06-004 examined the dose proportionality of FSS and determined the effects of temperature and pH on the pharmacokinetic parameters of five doses of FSS (100, 200, 400, 600 and 800 µg). Healthy individuals (n=67) were enrolled in the study. Somnolence was experienced by a maximum of 10% of individuals (n=2) at the 400, 600, and 800 µg doses of FSS.

In study INS-09-011 the absorption and distribution of 100 µg FSS in cancer patients both with and without oral mucositis were examined. Subjects (n=18) were enrolled in the study. No abuse-related AEs were reported.

Study INS-05-001 was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of FSS for breakthrough cancer pain. In this study, subjects were titrated up to their final dose of FSS. Of the 130 subjects enrolled in the titration phase, 98 (n = 98) successfully titrated into the double-blind portion of the trial.

Study INS-06-007 was an open-label, multicenter trial of FSS for the treatment of breakthrough cancer pain in opioid-tolerant patients. New (de novo) subjects and subjects that completed INS-05-001 were enrolled in the study. The de novo subjects were titrated up to an individualized dose of FSS over a period of 21-26 days. Once titrated, subjects were allowed a maximum of four doses of FSS over a 90 ± 5 day period.

In the pivotal clinical trials for the FSS product (INS-05-001 and INS-06-007) subjects were instructed to return all devices (both used and unused) back to the study site for documentation. According to the Sponsor, the “vast majority” of unreturned devices were inadvertently discarded by either the patient or caregiver. In two instances, devices were believed to be stolen.

Overall, 87,632 units were dispensed across the two trials and 1,223 were not returned (1.4%). Of the 359 unique subjects, 77 did not return at least one device (21%). A total of 26 subjects were discontinued from the pivotal studies. Seven subjects were discontinued due to “failure to comply with the administrative requirements of the protocol”. Two subjects were discontinued due to a “significant protocol violation”. Six subjects were discontinued due to “unable to determine a successful dose during titration”. Eleven subjects were discontinued due to “other”. According to the Sponsor, 24 of the 26 patients returned 100% of their study medication. One subject (subject 222-002) was discontinued for being under the influence of narcotics. The CRF was unclear as to whether “narcotics” included the study drug.

C. Integrated assessment

1. Findings

From an abuse potential perspective, the major risk associated with FSS is inadvertent exposure or dosing of children, pets, and unsuspecting individuals. The FSS unit appears innocuous and benign. The non-harmful appearance of FSS may result in,

mishandling (e.g., accidental discharge) or careless disposal. Prominent labeling on the FSS device may decrease the risk that a device will be unattended to or unaccounted for, and decrease the risk of accidental exposure of FSS (both used and unused devices) to children, pets, and individuals.

In a focus group study, (study INS-10-013) participants were provided a used FSS device and asked to identify it. Subjects produced 83 different ideas, including identifying the FSS device as a medical product, personal grooming product, childcare device, toy, food/candy dispenser, and safety device. These results demonstrate that without appropriate warning labels and identification, used and unused FSS devices are not readily identifiable. In addition, the same study found that individuals were incapable of distinguishing used (actuated or spent) devices from unused product, and that children identified the device as candy. Finally, one of the study participant's occupation was working with recovering drug addicts. This individual commented that motivated individuals will collect used devices in an attempt to extract medication from them.

There is also the risk of manipulation of the product (e.g. disassembly) for the purpose of injection. The sample units received by the reviewer were easy to take apart and separate into individual components. Separating the FSS unit into individual parts reveals an "injection ready" fentanyl solution that does not require preparation (i.e. extraction or purification) prior to i.v. administration. The fentanyl solution is highly attractive to a drug abuser, conferring a high abuse potential to FSS.

Based on the attractiveness of the fentanyl solution, we recommend the Sponsor redesign the FSS unit so that manipulation and disassembly of the FSS device is more difficult, and the FSS device is more secure.

III. References

Baylon GJ, Kaplan HL, Somer G, Busto UE, Sellers EM (2000) Comparative abuse liability of intravenously administered remifentanyl and fentanyl. *J Clin Psychopharmacol* 20:597-606

Broadbear JH, Winger G, Woods JH (2004) Self-administration of fentanyl, cocaine and ketamine: effects on the pituitary-adrenal axis in rhesus monkeys. *Psychopharmacology (Berl)* 176:398-406

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/s/

CHAD REISSIG
11/30/2011

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11/30/2011

MICHAEL KLEIN
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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: September 16, 2011

TO: Kathleen Davies, Regulatory Project Manager
Luke Yip, Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products

FROM: John Lee, M.D.
Medical Officer
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THROUGH: Susan Thompson, M.D.
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THROUGH: Jean Mulinde, M.D.
Acting Branch Chief
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SUBJECT: Evaluation of Clinical Inspections

NDA: 202-788

APPLICANT: Insys Therapeutics, Inc.

DRUG: Fentanyl Sublingual Spray (no trade name)

NME: No

INDICATION: Management of breakthrough cancer pain in opioid-tolerant adults

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: April 18, 2011

INSPECTION SUMMARY GOAL DATE: November 1, 2011

DAAAP ACTION GOAL DATE: January 4, 2012

PDUFA DUE DATE: January 4, 2012

I. BACKGROUND

Pain typically fluctuates, and significant flares beyond the otherwise adequately controlled background pain are called *breakthrough pains* (BP). When precipitated by voluntary action (such as movement), breakthrough pains are further specified as *incident pains* (IP). In cancer, breakthrough and incident pains remain important clinical problems that compromise health-related quality of life (HR-QoL). In cancer patients on long-term opioid therapy, BP and IP are commonly managed using a short-acting analgesic as-needed, commonly morphine sulfate, oxycodone, or hydromorphone.

Fentanyl (synthetic phenyl piperidine derivative) is an opioid receptor agonist with analgesic potency approximately 80-100 times that of morphine. Fentanyl has been marketed for over 30 years with a long record of safety and efficacy in pain management. Because of its potency, the expected adverse effects of somnolence and hypoventilation need to be continuously monitored when administered intravenously. Fentanyl is currently available as intravenous, intramuscular, and epidural injections, and as transdermal and oral (transmucosal) delivery formulations. The efficacy of fentanyl citrate is well documented.

- Following parenteral administration, fentanyl citrate has a rapid onset and short duration of action. It is metabolized in the liver by N-dealkylation and hydroxylation, and the metabolites (and some unchanged drug) are mostly excreted in the urine. The short duration of action is thought to be due to rapid tissue distribution, rather than rapid metabolism and excretion; an elimination half-life of about 4 hours reflects slow release from tissue. About 80% of the drug is bound to plasma proteins. Fentanyl appears in the cerebrospinal fluid, readily crosses into the placenta, and small amounts have been detected in breast milk. Buccal absorption is rapid with bioavailability in humans of about 50%. Between intravenous and buccal routes, no difference has been observed in the terminal elimination half-life.
- Sublingual fentanyl citrate appears to be safe, well tolerated, and effective in managing cancer BP pain, with many clinical advantages including ease of use, quick onset of action, and no associated drowsiness. The pharmacokinetics, safety, and tolerability of fentanyl citrate as a sublingual spray have been studied in healthy male volunteers under 55 years of age, under fasting conditions. The doses studied (100, 400, and 800 mcg) showed well-defined proportional pharmacokinetics. The side effects noted were typical of other opiates without any reported serious adverse event.
- The safety and efficacy of Fentanyl Sublingual (SL) Spray in managing cancer BP was initially evaluated among opioid-tolerant patients requiring, for a week or longer, at least: 60 mg oral morphine daily, 30 mg oral oxycodone daily, 8 mg oral hydromorphone daily, 25 mcg transdermal fentanyl hourly, or an equianalgesic dose of another opioid. Fentanyl had good absorption in as little as 2.5 minutes after administration (high lipid solubility at natural pH of sublingual cavity). Fentanyl SL Spray was not associated with adverse taste, as has been the case with some opioids.

INS05-001 was a phase 3, randomized, double-blind, placebo-controlled study conducted at 21 US centers (130 patients) to evaluate the safety and efficacy of Fentanyl SL Spray in managing cancer BP. Patients on a stable dose of opioid medication and experiencing up to 4 episodes of BP per day were enrolled into the study. The minimum dose for adequate analgesia for each patient was identified during the initial open-label titration period of the study. During the subsequent double-blinded period, each patient was given 10 blinded doses of Fentanyl SL Spray

to manage BP, 7 active and 3 placebo doses in random order. After each dose, pain intensity was measured at 5, 10, 15, 30, 45 and 60 minutes using a visual analog scale (score range 0 - 100), and pain intensity difference (PID) was calculated by subtracting the pain intensity at baseline (time 0) from the pain intensity at each time point. The primary efficacy endpoint was defined as the sum of the PID scores through the 30-minute time point, or Summed Pain Intensity Difference through 30 minutes (SPID 30).

II. INSPECTION RESULTS

Three good clinical practice (GCP) inspections of Study INS05-001 were conducted in support of this NDA review, as summarized in the table below. The inspected clinical sites were selected based on large subject enrollment and/or high rate of reported protocol violations.

	Inspected Entity	Protocol Site / Subjects	Inspection Dates	Classification
1	Janet Bull, MD 571 South Allen Rd Flat Rock, NC	INS05-001 Site 142 20 enrolled	May 23 - 26, 2011	NAI
2	Richard L. Rauck, MD 145 Kimel Park, Suite 330 Winston-Salem, NC	INS05-001 Site 120 10 enrolled	June 6 - 7, 2011	NAI
3	W. Keith Lara, MD 195 Commons Loop, Suite F Kalispell, MT	INS05-001 Site 109 10 enrolled	June 1 - 7, 2011	VAI

Classification: NAI = no deviation from regulations
VAI = deviation from regulations
OAI = significant deviation from regulations and/or data unreliable

1. Janet Bull (Site 142)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications

- Subjects: 20 subjects were screened, 20 were enrolled into the study, and 17 completed the study. Subject records were reviewed in detail, to include the primary efficacy endpoint and adverse events, for all 20 enrolled subjects.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
 - Primary endpoint data were verifiable; the data matched among source records, case report forms, and data listings reported in the NDA. Underreporting of adverse events was not observed.
 - All subjects at this site appeared to have been administered informed consent properly prior to study enrollment. The list of protocol violations matched those noted in subject records. Source records appeared factual and complete, and matched corresponding case report forms. Drug accountability was well documented. No significant objectionable conditions were observed.
- c. Assessment of data integrity: Data from this study site appear reliable.

2. Richard L. Rauck (Site 120)

- a. What was inspected:
- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
 - Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications
 - Subjects: 10 subjects were screened, 10 were enrolled into the study, and 10 completed the study. Subject records for all 10 subjects were reviewed to include informed consent, primary efficacy endpoint, and adverse events.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
 - Primary endpoint data were verifiable; the Pain Intensity data reported by the subjects at 0, 5, 10, 15, and 30 minutes matched among source records, case report forms, and data listings reported in the NDA. No discrepancies were noted. Underreporting of adverse events was not observed.
 - All subjects at this site appeared to have been administered informed consent properly prior to study enrollment. The list of protocol violations matched those noted in subject records. Source records appeared factual and complete, and matched corresponding case report forms. Drug accountability was well documented. No significant objectionable conditions were observed.
- c. Assessment of data integrity: Data from this study site appear reliable.

3. William Keith Lara (Site 109)

- a. What was inspected:
 - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
 - Data verification: primary endpoint, adverse events, subject randomization, protocol deviations, subject discontinuations, concomitant medications
 - Subjects: 11 subjects were screened, 10 were enrolled into the study, and 8 completed the study. Subject records for all 10 enrolled subjects were completely reviewed.
- b. General observations and comments:
 - The study appeared to have been generally conducted according to GCP standards and regulations. The study data were well-organized. IRB oversight and study monitoring appeared to be adequate.
 - Primary endpoint data were verifiable; the data matched among source records, case report forms, and data listings reported in the NDA supplement. Underreporting of adverse events was not observed.
 - All subjects at this site appeared to have been consented properly prior to study enrollment. Source records appeared factual and complete, and matched corresponding case report forms.
 - A Form FDA 483 was issued for: (1) not having the Delegation of Authority adequately documented for 3 study personnel, (2) not reporting 3 protocol deviations (2 dosing errors, 1 instance of not completing the Treatment Satisfaction Questionnaire for Medication) to the IRB, and (3) failing to re-obtain informed consent from one subject after revision of the consent form using the most recent IRB-approved version.
- c. Assessment of data integrity: Form FDA 483 observations are considered minor deficiencies that appeared to be isolated instances, which are not expected to affect the study outcome. Overall, data from this study site appear reliable and to have been accurately reported in the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this NDA review, the conduct of Study INS05-001 was inspected at three clinical study sites. The study sites were selected for inspection based on large numbers of subject enrollment and/or reported protocol violations.

A Form FDA 483 was issued at Site 109 (Lara) for isolated minor GCP deficiencies and this inspection was classified as Voluntary Action Indicated (VAI). The minor regulatory violations identified at this site are unlikely to impact efficacy or safety analyses. Therefore, OSI does not consider the effect on overall data integrity to be significant. No significant deficiencies were observed and a Form FDA 483 was not issued at Sites 142 (Bull) and 120 (Rauck); these inspections were classified as No Action Indicated (NAI).

At all three sites, the overall adherence to GCP was considered acceptable; the study appeared to have been conducted in accordance with the study protocol and applicable GCP regulations (with

minor isolated exceptions as noted for Site 109), including data collection and assurance of subject safety and welfare. The study data reviewed at the three inspected clinical study sites appear reliable with respect to the study protocol as written and submitted to the NDA.

{See appended electronic signature page}

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**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: August 29, 2011

To: Bob Rappaport, MD, Director
Division of Analgesia and Anesthesia Products

Through: Lubna Merchant, PharmD., M.S., Team Leader
Kellie Taylor, PharmD, MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne Crandall Tobenkin, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s) and Strengths: Subsys (Fentanyl) Sublingual Spray, 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg per spray

Application Type/Number: NDA 202788

Applicant: Insys Therapeutics

OSE RCM #: 2011-1019

1 EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis' evaluation of both the labels and labeling as well as the Label Comprehension and the Design Failure Mode and Effects Analysis (DFMEA) for medication error potential and usability of the device in the usual practice setting.

Our evaluation of the labels and labeling identified several safety issues, such as the control substance statement and ingredient per unit are not communicated on the labels and labeling which may cause confusion during use of the product and result in medication errors. We provide recommendations to mitigate confusion in Section 4.2 which should be implemented prior to approval.

Furthermore, the submitted studies identified problems with several stages of device use and determined that the provided instructions resulted in confusion during dosing. Although the instructions were revised as a result of the identified confusion, we recommend testing the revised instructions on a new population to ensure they adequately communicate safe instructions for use.

2 PRODUCT INFORMATION

Subsys sublingual spray is indicated for the management of breakthrough cancer pain in opioid-tolerant patients. Subsys will be available as 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg per spray single use bottles which are contained in individually sealed child-resistant blister packages. The recommended starting dose is 100 mcg. The usual dose is 1 or 2 sprays sublingually administered at no more than every four hours. The maximum daily dose is 6400 mcg. Subsys will be supplied as a single use spray device in cartons of 6, 14 and 28. Subsys will also include a (b) (4) disposal system, however based on the submission dated March 4, 2011, we are unable to ascertain if this disposal system will be included in each carton or separately.

3 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product design and product container labels, carton and insert labeling submitted on March 4, 2011 to identify vulnerabilities that may lead to medication errors. See Appendix A for samples of the draft container labels and carton labeling.

Additionally, the Applicant submitted a Label Comprehension Report and Disposal and a Design Failure Modes and Effects Analysis (DFMEA) for a Unit-Dose Fentanyl Sublingual Spray. The Applicant intended to demonstrate that the intended user of the device can follow directions and use Subsys based on the Instructions for Use and that the device is safe for use.

4 RESULTS AND DISCUSSION

The following sections discuss the results and discussion that pertain to the Subsys container labels, carton and insert labeling as well as the studies submitted with the Subsys labels and labeling.

4.1 CONTAINER LABELS

The container labels lack information such as the control substance symbol. Additionally, because of the small size of the container and container label, the label must state the proprietary name, established name, lot number and name of manufacturer in order to be in compliance with 21 CFR 210.10(i).

4.2 CARTON LABELING

The carton labeling lacks information such as the control substance symbol and Medication Guide statements. Additionally, the strength statement is incomplete because it is not identified as ‘per spray’ throughout the label and labeling. Furthermore, pertinent information such as dosing instructions, route of administration are not prominent and therefore may not be seen by the patient or practitioner.

4.3 INSERT LABELING

The insert labeling uses the term ‘dose’ and ‘spray’ interchangeably, however, these terms have different definitions because a dose can be equal to one or two sprays. This inconsistent use of terminology can result in confusion because patients can use two sprays to equal one dose in the titration period. Per the instructions, patients should wait four hours in between doses however another spray can be utilized after one half hour during titration. Using these terms interchangeably can result in patient confusion about when the next spray or dose can be utilized resulting in overdose or decreased pain control.

Additionally, the Applicant’s analysis only included patients that were not physically impaired. Although this was not elaborated on or defined further, we noted during our interaction with the device and overwrap that a high level of dexterity is required to open the blisters and activate the sublingual device. This requirement should be communicated to the prescriber, as patients with impaired dexterity would be better suited for other fentanyl dosage forms.

4.4 DESIGN FAILURE MODES AND EFFECTS ANALYSIS (DFMEA)

The submitted DFMEA focused more on mechanical failures that could occur with the device, as opposed to user errors that could occur when the patient interacts with the device. There was very little to no safety or medication error device evaluations in this DFMEA, and is more applicable to analyses that are performed by CDRH.

4.5 LABEL COMPREHENSION STUDY

The Label Comprehension Study involved patient interaction with the device and assessed the potential for medication error and safety, therefore DMEPA has comments regarding this study. The Label Comprehension Study measured (established success

and failure criteria) how well an intended user can follow the provided directions and use Fentanyl sublingual spray based on the content in the Instructions for Use and Disposal. If the respondent sprayed the product away from the mouth, it was classified as ‘failing to use product correctly’ and if the respondent did not dispose of the unit by sealing it in the disposal bag, it would be classified as ‘failing to dispose of the product safely’. The desired success rate was determined to be 90% and the study included 30 participants. According to the submission, “nearly all (90%) used it correctly on their first attempt. All (100%) used it correctly on their first or second attempt. All respondents attempted to dispose of the unit correctly”. Our assessment of the study is detailed below in Sections 3.5.1 to 3.5.3.

4.5.1 Device Orientation

The study results demonstrate user error with respect to orientation of the device. One participant held the device upside down and sprayed the device unaware that it was upside down resulting in no dose ingested. Two other participants, both female, had trouble depressing the device which resulted in one spraying the device in the air and the other on his lower lip and chin, when prompted to refer to the diagram she still was unable to hold the device correctly and had to be shown by a test administrator. Additionally, one participant verbalized that not all the spray went into his mouth and some got on his lip. Based on the reported results, the instructions were revised to present the instructions in a bulleted format and given to the respondents, which then correctly targeted the drug under the tongue. However, because the respondents received instruction from the administrator and had previously sprayed the device, it is difficult to ascertain if the instructions improved performance or if the patient was more familiar with the product and therefore less prone to make an error.

4.5.2 Device Disposal

The study results demonstrated that confusion can occur with disposal which may result in accidental exposures. Two out of thirty patients performed errors such as not sealing the bag or tearing the bottom of the bag. The study did not report if the bag or the instructions on the bag were revised to more clearly indicate how to properly use and dispose of the product and if the revisions rectified the confusion.

Additionally, the bags will be discarded in the trash rather than flushed. Although we do not recommend a statement alerting that a controlled substance is contained in the pouch, we do have concerns that there is no statement alerting that the pouch contains a dangerous substance that should be kept away from children and pets and should not be ingested. Our concerns were conveyed to the Controlled Substance Staff (CSS) in a meeting held July 7, 2011. We defer to their expertise in regards to the safety and regulatory requirements for this disposal system.

4.5.3 Comprehension of Dosing Directions and Warnings

The study moderators verbally questioned patients to determine if the participants understood how to properly dose the product. According to the instructions for use, Subsys should be dosed every four hours. However, based on the study results, almost half of the patients were confused about when another dose could be administered.

Eighteen of the respondents replied 30 minutes and 12 respondents replied four hours. Analysis of the instructions that were submitted to the Agency determined that the terms ‘dose’ and ‘spray’ are used interchangeably which may have contributed to this confusion. A spray is a singular action which can be repeated in a half hour, whereas a dose can consist of one or two sprays. The instructions should be revised to clearly define and differentiate between a spray or a dose. Additionally, these instructions should be re-tested to ensure that they more clearly differentiate between a dose and a spray and that patients are able to understand and administer a dose or spray at the correct time intervals.

5 CONCLUSIONS AND RECOMMENDATIONS

Our analysis of the proposed Subsys device determined that there are design features that minimize the risk of overdose medication errors with Fentanyl. However, our analysis of the submitted label study uncovered several use errors, which resulted in label revisions, however these revisions were not re-tested to demonstrate that the revisions adequately addressed the user errors. Thus, we have no conclusive evidence to support the revisions improved the usability of the product. Our evaluation of the labels and labeling identified several areas that may cause confusion during use and result in medication error. Furthermore, we also noted that the proposed disposal of Subsys does not align with current federal guidelines for control substances, however, we defer to CSS for the acceptability of this proposed disposal.

We provide recommendations on the insert labeling in Section 5.1 Comments to the Division. Section 5.2 Comments to the Applicant contains our analysis of the submitted studies and recommendations for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to Insys prior to the approval of this NDA.

Please copy the Division of Medication Error Prevention and Analysis on any communication to (b) (4) with regard to this review. If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE Project Manager, at 301-796-3813.

5.1 COMMENTS TO THE DIVISION

1. The term spray and dose are used interchangeably which may get confusing for both practitioners and patients, especially when instructed to wait at least 4 hours between doses, but ‘No more than two doses can be taken per breakthrough cancer pain episode’.
2. The insert should communicate in the precaution section (example provided, Symlin insert) that Subsys should be prescribed with caution in patients with impaired dexterity.
3. DMEPA is concerned that the disposal strategy for this device, which contains residual drug product in an unmarked pouch, could be dangerous because there is no statement that alerts consumers or healthcare providers that the

pouch contains a dangerous product. This may lead to accidental drug exposures. Additionally, because some fentanyl products are on the flush list, the disposal strategy for this fentanyl product may not be in compliance with federal guidelines.

5.2 COMMENTS TO THE APPLICANT

A. Label Comprehension Study

1. Your submission did not indicate if the disposal bags or instructions for disposal were revised to mitigate errors seen in the study with regards to not sealing the bag and correctly opening the bag (tearing bag) and the possible outcome of unintended exposure. The study should have assessed if the errors occurred due to inadequate instructions for use or if the patients did not completely understand the instructions. If the bags or instructions were revised they should be re-tested, to determine that the revisions have improved the instructions for use.
2. The submitted study identified confusion regarding re-dosing the product if the pain is not relieved. This confusion could be occurring because the terms ‘spray’ and ‘dose’ are used interchangeably. These two terms should be clearly defined and consistently utilized throughout the instructions to avoid confusion between the two terms. The revised instructions should be re-tested in order to ensure safe use, especially in patients that are naïve to Subsys administration and use.
3. The revised instructions should be tested on a new set of users to ensure that they address the confusion that resulted in administration errors (wrong orientation and problems depressing device) identified during the first study prior to approval.

B. General Comments for all labels and labeling

1. The strength statement should be followed by the statement ‘per spray’.
2. Include a ‘CII’ statement on all container labels, blister, and carton labeling, wherever the tradename and established name appear in accordance with 21 CFR 1302.03.

C. Container Labels

1. Revise the color block so that it highlights the proprietary name, established name and strength only and does not include the NDC number.
2. Include the ‘Rx Only’ statement on the label on the principal display panel.
3. Include the lot and expiration statements on the side panel of the label.

D. Overwrap Labeling (All strengths)

1. Revise the color block so that it incorporates the proprietary name, established name and strength and does not include the NDC number or the Rx Only statement. Additionally, relocate the Rx Only statement so that it appears where the Quantity statement is currently located on the principal display panel.
2. Increase the prominence of the established name which includes ‘sublingual spray’ to ensure that the route of administration is communicated to the patient.
3. Revise the quantity statement so that it reads ‘the enclosed device contains one spray’. Additionally, increase the font and prominence of the quantity statement and relocate the statement so that it appears above the boxed warning on the principal display panel.
4. Include a statement under the route of administration statement which instructs to refer to the Med Guide for instructions for use.
5. Relocate the ‘Use immediately after opening’ statement so that it appears below the ‘For administration under the tongue. Dosing must be at least 4 hours apart.’
6. Bold the statements, ‘For administration under the tongue. Dosing must be 4 hours apart.’
7. Relocate the storage statement so that it appears below the red warning box and decrease the prominence of the statement so that it does not compete with other pertinent safety and dosing information.
8. Decrease the size, prominence and coloring of the ‘Insys’ statement.
9. Relocate the ‘Rx Only’ statement to the bottom of the Principal display panel so that there is no interfering matter between the established name and the strength.

E. Carton Labeling (all strengths and quantities: 6, 14, 28)

1. Revise the quantity statement so that it reads;
This carton contains XX devices
Each device contains one spray
2. Relocate the quantity statement on the top of the side panel so that there is no interfering matter between the established name and the strength statement. Additionally, the quantity statement should appear on the top panel.

3. Relocate the 'Rx Only' statement so that it is less prominent and revise the statement so that it does not appear boxed.
4. In the current labels, the strength statement gets lost because it competes with the warning statements on the side panel. Revise the strength statement on the side panel to increase the prominence.
5. Per the submitted REMS, Susbsys will be dispensed with a Med Guide, therefore the principal display panel should display the approved Medication Guide statement.
6. Because the carton could be stored multiple ways on a pharmacy shelf, include the warnings (Med Guide, etc.) on both the flap panel and the top panel of the carton to ensure they are visible and therefore communicated from multiple angles.
7. Delete the statement on the flap panel, 'Use immediately after opening' as the statement is ambiguous and not applicable to the carton labeling.
8. Delete the redundant temperature recommendations on the flap panel, as they are clearly stated on the back panel.
9. Use bold font for the statements, 'For administration under the tongue only. Dosing must be 4 hours apart.' and relocate these statements to the where the temperate statements are currently located on the flap panel. This dosing instructions should also appear on the top panel.
10. Include a statement on the flap panel which alerts practitioners that Subsys should not be substituted for other Fentanyl products.
11. Decrease the size and prominence of the 'Insys' statement.
12. Relocate the 'Rx Only' statement so that there is no interfering matter between the established name and the strength.

F. Disposal pouch

Include instructions on the pouch which detail how to properly open and seal the bag. Additionally, include a statement warning that the contents in the pouch should not be ingested.

G. Disposal system

1. It is not clearly stated as to how the disposal system will be dispensed. Will this be included in cartons? If not, how will a pharmacist know to dispense the system? How will they be stored? Please explain.
2. The (b) (4) top on the (b) (4) disposal system is inappropriate for the intent of the bottle, which is to make the drug product inaccessible and unusable. However, this top can be easily removed or misplaced. Therefore, we request the top be firmly attached to the bottle.

18 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS)
immediately following this page

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

/s/

ANNE C TOBENKIN
08/29/2011

LUBNA A MERCHANT
08/29/2011

KELLIE A TAYLOR
08/29/2011

CAROL A HOLQUIST
08/29/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 202788 BLA#	NDA Supplement #:S- BLA STN #
Efficacy Supplement Type SE-	
Proprietary Name: Subsys (proposed) Established/Proper Name: fentanyl Dosage Form: sublingual spray Strengths: 100, 200, 400, 600, 800 mcg	
Applicant: Insys Therapeutics, Inc. Agent for Applicant (if applicable): The Weinberg Group, Inc.	
Date of Application: March 4, 2011 Date of Receipt: March 4, 2011 Date clock started after UN:	
PDUFA Goal Date: January 4, 2012	Action Goal Date (if different):
Filing Date: May 3, 2011	Date of Filing Meeting: April 13, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3 – new dosage form.	
Proposed indication(s)/Proposed change(s): management of breakthrough cancer pain in opioid tolerant patients.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 72411				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>NDA 22266</td> <td>Onsolis</td> <td>NP</td> <td>July 16, 2012</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	NDA 22266	Onsolis	NP	July 16, 2012									<p>X</p>			<p>NDA 22266 (onsolis) Has unexpired exclusivity</p>
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
NDA 22266	Onsolis	NP	July 16, 2012																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff: 3/30/11</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		X		Will be requested in 74-day letter

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			DSI – Sent 4/20/11
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): December 17, 2007 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 17, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 13, 1011

BLA/NDA/Supp #: 202788

PROPRIETARY NAME: Subsys (proposed)

ESTABLISHED/PROPER NAME: fentanyl

DOSAGE FORM/STRENGTH: sublingual spray, 100, 200, 400, 600, 800 mcg

APPLICANT: Insys Therapeutics, Inc., (c/o) The Weinberg Group, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of breakthrough cancer pain in opioid tolerant patients.

BACKGROUND: Sponsor submitted a 505(b)(2) application to Actiq. This is a new dosage form, a sublingual spray.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kathleen Davies	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Sharon Hertz		Y
Clinical	Reviewer:	Luke Yip	Y
	TL:	N/A	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Yan Zhou	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Julia Pinto	Y
	TL:	Prasad Peri	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Brian Riley	N
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Anne Crandal	N
	TL:	Melina Griffis	N
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:	Barbara Fuller	N
OC/DCRMS (REMS)	Reviewer:	Doris Auth	Y
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	Chad Reissig	Y
	TL:	Sylvia Calderon	N
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob Rappaport 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

<input type="checkbox"/>	<ul style="list-style-type: none"> notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

KATHLEEN M DAVIES
05/11/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 28, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

Subject: **NDA 202788 Fentanyl Sublingual Spray**
Indication: Breakthrough cancer pain
Dosages: 100, 200, 400, 600 or 800 µg of fentanyl per (b) (4) spray.
Sponsor: Insys Therapeutics

Materials reviewed: NDA 202788 located at: \\ [\CDSESUB1\EVSPROD\NDA202788](#)
Previous IND review (72,411) by Jovita Randall-Thompson, Ph.D.

I. Summary

A. Background

Fentanyl sublingual spray is a new formulation of fentanyl intended for the treatment of breakthrough cancer pain. The pharmacological and analgesic effects of fentanyl are mediated primarily through mu-opioid receptors. The fentanyl sublingual spray contains the same active ingredient as other fentanyl products including oral, injectable, and transdermal products. The Sponsor is submitting their application through the 505(b)(2) pathway.

CSS was consulted to determine the filability of the NDA.

B. Conclusions and Recommendations

- From a CSS perspective, the NDA can be filed.
- The Sponsor has not performed an analysis of abuse-related adverse events. This is a review issue and will be addressed in the 74-day letter to the Sponsor.

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

/s/

CHAD REISSIG
04/28/2011

SILVIA N CALDERON
04/29/2011

MICHAEL KLEIN
04/29/2011