

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202788

SUPPL #

HFD # 170

Trade Name Subsys

Generic Name fentanyl sublingual spray

Applicant Name Insys Therapeutics

Approval Date, If Known Jan 4, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(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 fentanyl
ANDAs for complete list

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.**

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO X

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO X

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO X

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study INS-05-001, A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 72,411

YES X

!
!
! NO
! Explain:

Investigation #2

IND #

YES

!
!
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!
!
! NO
! Explain:

Investigation #2

YES

Explain:

!
!
! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO X

If yes, explain:

=====
Name of person completing form: Sharon Hertz, M.D.
Title: Deputy Director
Date: 12/28/11

Name of Office/Division Director signing form: Bob A. Rappaport, MD
Title: Director

RPM: S. Stradley 12/28/11

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

/s/

SARA E STRADLEY
01/03/2012

BOB A RAPPAPORT
01/04/2012

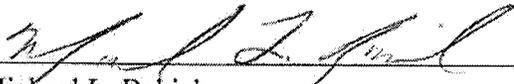
Debarment Certification

**CERTIFICATION PURSUANT TO SECTION 306(K)(1) OF THE GENERIC DRUG
ENFORCEMENT ACT OF 1992 [21 USC § 335A(K)(1)]**

This is to certify:

- (1) that Insys Therapeutics, Inc. did not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with the development or submission of this application;
- (2) that Insys Therapeutics, Inc. will not use in any capacity the services of any person debarred under subsection (a) or (b) if this section in connection with this application; and
- (3) that neither Insys Therapeutics, Inc. nor affiliated persons responsible for the development or submission of this application have been convicted within the past five (5) years of offenses described in subsections (a) and (b) of this section.

List of convictions: None



Michael L. Babich
President & Chief Operating Officer
INSYS THERAPEUTICS, INC.



Date

From: [Davies, Kathleen](#)
To: [Stradley, Sara](#); [Hertz, Sharon H](#); [Yip, Luke](#); [Qiu, Wei](#); [Xu, Yun \(CDER\)](#)
Subject: FW: NDA 202-788 Fentanyl SL Spray
Date: Friday, December 09, 2011 9:35:49 AM
Attachments: [1_Pediatric_Record.pdf](#)
Importance: High

From: Greeley, George
Sent: Friday, December 09, 2011 9:35 AM
To: Davies, Kathleen
Cc: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Rappaport, Bob A
Subject: NDA 202-788 Fentanyl SL Spray
Importance: High

Hi Kathleen,

The email serves as confirmation of the review for the Fentanyl Sublingual Spray product conducted by the PeRC PREA Subcommittee on December 7, 2011.

The Division presented a full waiver in patients for the indication of management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer because there are too few children with disease/condition to study.

The PeRC agreed with the Division to grant a full waiver for this product.

The pediatric record is attached for Fentanyl.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.

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

/s/

SARA E STRADLEY
12/17/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202788 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Subsys Established/Proper Name: fentanyl sublingual spray Dosage Form: sublingual spray		Applicant: Insys Therapeutics Agent for Applicant (if applicable):
RPM: Kathleen Davies and Sara Stradley		Division: DAAAP
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		
<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Actiq (NDA 20747)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>new dosage form</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p>X No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>		
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>1/4/2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments: REMS included Evidence of Safe Use Conditions, Implementation System, MG, Pharmacy/Healthcare Setting Certification, Prescriber Training or Certification</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 1/4/2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	see AP letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	see AP letter
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	original included
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	6/7/2011 11/8/2011, 6/7/2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	X DMMP 12/8/2011 X DMEPA 8/29/2011 X DRISK (See REMS) X DDTCP 12/8/2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	5/11/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 1/3/2012
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) 1/4/2012
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included 1/4/2012
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes X No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes X No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>12/7/2011</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	X Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	various dates
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	X N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	X 8/17/2010
• EOP2 meeting (<i>indicate date of mtg</i>)	X 12/17/2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	no
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	X None
Division Director Summary Review (<i>indicate date for each review</i>)	X 1/4/2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X 12/28/2011
PMR/PMC Development Templates (<i>indicate total number</i>)	X None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	see CDTL memo
• Clinical review(s) (<i>indicate date for each review</i>)	12/15/2011, 5/2/2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	in clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X 12/21/2011, 11/30/2011, 4/29/2011
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	Dec 28, 2011 1/2/2011 X DRISK, 12/30/2011
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	X

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		X None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		X None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		X None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		X None
Statistical Review(s) <i>(indicate date for each review)</i>		X 11/30/2011, 5/3/2011
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		X None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		X None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		X 11/30/2011, 4/18/2011
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>		X None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		X None
• Supervisory Review(s) <i>(indicate date for each review)</i>		X None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		X 11/30/2011, 4/15/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>		X None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		X No carc
❖ ECAC/CAC report/memo of meeting		X None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>		X None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		X None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		X None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		X 12/28/2011, 11/21/2011
❖ Microbiology Reviews		X 9/7/2011, 5/4/2011
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		X None

❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	CMC review, page 63
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
X NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁶)	Date completed: 4/18/2011 X Acceptable (page 58 of CMC review) ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (original and supplemental BLAs)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested X Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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

/s/

SARA E STRADLEY
01/05/2012

Stradley, Sara

From: Stradley, Sara
Sent: Tuesday, January 03, 2012 12:20 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: comments on carton and container

Hi Lauren

In order to link the PI and MG labeling to the carton and container labeling, we need the following changes to be made to the carton and container labeling

Carton (the example below is for the 100 mcg unit)

"Each spray device unit contains 100 mcg of fentanyl base, dehydrated alcohol 63.6%....."

"This carton contains 28 device units. Each device unit contains one spray"

Container (the example below is for the 100 mcg unit)

"Quantity: The enclosed device unit contains one spray"

Comments on PI and MG will be coming shortly

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
01/03/2012

Stradley, Sara

From: Compton, Kimberly
Sent: Tuesday, December 27, 2011 6:09 PM
To: 'Lauren Wind'
Cc: Jani, Parinda; Stradley, Sara
Subject: FW: FDA redline copy 122711_SH Insys.doc

Attachments: FDA redline copy 122711_SH Insys.doc

Hi Lauren,

We have accepted a number of proposed changes and deleted the associated comments.

Some of the proposed changes to the description and PK section were promotional in tone and removed.

The final review of the clin pharm additions is pending return of the reviewers.

For the clinical trials section, [REDACTED] (b) (4) This is consistent with other labels of the class. [REDACTED] (b) (4)

If you would like to discuss any of the changes let us know and we will set up a call.



FDA redline copy
122711_SH Ins...

Thanks,

Kim for Parinda and Sara

28 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/

SARA E STRADLEY
12/28/2011

From: [Compton, Kimberly](#)
To: ["Lauren Wind"](#)
Cc: [Stradley, Sara](#)
Subject: FW: TIRF REMS "Gold standard" for Insys
Date: Thursday, December 22, 2011 4:11:31 PM
Attachments: [chain-pharm-enrollment-form.doc](#)
[chain-pharm-overview.doc](#)
[distributor-enrollment-form.doc](#)
[distributor-letter.doc](#)
[education-program.ppt](#)
[faq.doc](#)
[hcp-letter.doc](#)
[inpatient-pharm-enrollment-form.doc](#)
[inpatient-pharm-letter.doc](#)
[inpatient-pharm-overview.doc](#)
[knowledge-assessment.doc](#)
[outpatient-pharm-enrollment-form.doc](#)
[outpatient-pharm-letter.doc](#)
[outpatient-pharm-overview.doc](#)
[patient-and-caregiver-overview.doc](#)
[ppaf.doc](#)
[prescriber-enrollment-form.doc](#)
[prescriber-overview.doc](#)
[rems.doc](#)
[supp-doc-word.doc](#)
[website.pdf](#)
[111130_TIRF_REMS_Submission_Instructions.docx](#)
Importance: High

Hi Lauren,

Attached are the "Gold Standard" TIRF REMS documents, including the Supporting Document and the Web Prototype for Insys to submit to their Subsys NDA ASAP. Please let them know of the following:

1. We have edited the documents to include Subsys in the REMS materials; however, they should review everything thoroughly as we were not able to update the TIRF Education Program and the Web Prototype to include Subsys. They should update these documents. Furthermore, the Outpatient Pharmacy Enrollment form and the Chain Pharmacy Enrollment form need to be verified to ensure that the NDC numbers for Subsys are included in the "contract agreement" section of the forms, as applicable.
2. There were typos in some of the REMS materials that were communicated to the TRIG this morning (12/22) and are reflected in the attached documents as track changes. For reference, the list of typos are also provided below. Please note, the corrections to the REMS Supporting document were not included in our correspondence this morning.
3. Attachment 1' is replaced with the existing Attachment 1 in the "Overview for Patient and Caregivers", as the additional information in the 'healthcare provider version' is not necessary.
4. Attached are the submission instructions.

Following are list of Typos:

1. Education Program for Prescribers and Pharmacists -- Page 7
First bullet - "... in adult patients with cancer 18 years of ..." [delete the second "with cancer"]
2. Knowledge Assessment -- Page 1 - Question 2 - Answer B
"and reconstructive" rather than "andreconstructive"
3. Dear Healthcare Provider Letter

a. Page 5 - Adverse Reactions, last two words - "... TIRF medicine." rather than "... TIRF medicines."

b. Page 6 - Second paragraph, second sentence - "Medication Guides will ..." rather than "Medication guides will ..."

4. Prescriber Overview - Page 1, first paragraph, fourth line - ")" rather than "))"

5. REMS Supporting Document

a. Page 19 - second paragraph, last word - "enrollment" rather than "enrolment"

b. Page 20 - last word - "medicine" rather than "medicines"

c. Page 25 - last sentence - "shown" rather than "show"

d. Page 26 - "TIRF NDA Sponsors" rather than "TIRF Sponsors"

e. Page 28

i. Figure 7 - "opioid" is misspelled twice

ii. Item 7 - "Assessment" rather than "Assessments"

f. Page 29 - Item 12 - "Assessment" rather than "Assessments"

B. The Timetable for Submission of Assessments within the REMS document has been updated to read "TIRF NDA Sponsor" rather than "TIRF Sponsors."

C. Based on the 12/21 T-con, 'Attachment 1' will be replaced with the the existing Attachment 1 in the "Overview for Patient and Caregivers", as the additional information in the 'healthcare provider version' (e.g. NDC numbers) is not necessary. However, this will not affect the inclusion of NDC numbers in Pharmacy Chain Enrollment form and the Outpatient Pharmacy Enrollment form; no changes will be made to these forms.

D. We have identified the following typos in the Web Prototype document. The Web Prototype document does not need to be updated at this time. The TRIG should ensure that these corrections are made before the actual website is launched.

a. Page 3 - Education Program, last line - "LOGGED" or "LOGGED IN" rather than "LOGED"

b. Page 4 - Chain Pharmacy Enrollment Process

"CHAIN PHARMACY ENROLLMENT CONFIRMATION" rather than "CHAIN ENROLLMENT CONFIRMATION"

c. Page 5

i. MY ACCOUNT - INPATIENT PHARMACY

"INPATIENT PHARMACY LOOKUP RESULTS" rather than "INPATIENT PHARMACY LOOKUP RESULT"

ii. MY ACCOUNT - OUTPATIENT PHARMACY

A). "OUTPATIENT PHARMACY LOOKUP" rather than "PHARMACY LOOKUP"

B). "OUTPATIENT PHARMACY LOOKUP RESULTS" rather than "PHARMACY LOOKUP RESULTS"

- d. Page 7
 - i. Adverse Reactions, last sentence - "... to each TIRF medicine." rather than "... to each TIRF medicines."
 - ii. Medication Guide, last paragraph, second sentence - "Medication Guides ..." rather than "Medication guides ..."
- e. Page 9
 - i. Paragraph which begins "When dispensing, ..." - Penultimate sentence - "... each time they begin ..." rather than "... each they begin ..."
 - ii. Adverse Reactions, last sentence - "... for each TIRF medicine." rather than "... for each TIRF medicines."
 - ii. Medication Guide, last paragraph, second sentence - "Medication Guides ..." rather than "Medication guides ..."
- f. Page 10 - Penultimate sentence - "Important Safety Information (ISI) is included ..." [add "(ISI)"]
- g. Page 18
 - i. First paragraph, last sentence - "the Providers" rather than ""the Providers"
 - ii. NDC numbers, fifth line - "55253-0072-30" and "55253-0073-30" rather than "55523-0072-30" and "55523-0073-30"
 - iii. Paragraph which begins "Pharmacy acknowledges ...", last sentence - "reserve" rather than "reserves"
- h. Page 52 - Boxed text - "TIRF medicines for" rather than "TIRF medinces for"
- i. Page 53 - Boxed text - "headquarters" rather than "headquaters"
- j. Page 62
 - i. First bullet, first sentence - "agonist" rather than "against"
 - ii. Fourth bullet - "opioids" rather than "opioid"
- k. Page 64 - Second bullet - "dangerous increase" rather than "dangerous increases"
- l. Page 68 - Lazanda, third column - "cancer breakthrough pain episode" rather than "breakthrough pain cancer episode"
- m. Page 70 - Tell the patient, sixth bullet - "medicine" rather than "medicne"
- n. Page 73, first line - "Logged" or "Logged in" rather than "Loged"
- o. Page 86 - The answers to the Knowledge Assessment are not correct as seen on this page - are they supposed to be?
- p. Page 93
 - i. First line - "medicines" rather than "medicinces"
 - ii. Item 1 - "each TIRF medicine prescribed" rather than "each TIRF medicines prescribed"

- q. Page 111
 - i. NDC numbers, fifth line - "55253-0072-30" and "55253-0073-30" rather than "55523-0072-30" and "55523-0073-30"
 - ii. Paragraph which begins "Pharmacy acknowledges ...", last sentence - "reserve" rather than "reserves"
- r. Page 122
 - i. NDC numbers, fifth line - "55253-0072-30" and "55253-0073-30" rather than "55523-0072-30" and "55523-0073-30"
 - ii. Paragraph which begins "Pharmacy acknowledges ...", last sentence - "reserve" rather than "reserves"
- s. Page 127 - The answers to the Knowledge Assessment are not correct as seen on this page - are they supposed to be?
- t. Page 132
 - i. Item 3 - "I intend to prescribe" rather than "I intend to prescribed"
 - ii. Last sentence - "state" rather than "states"
- u. Page 173 - NDC numbers, Anesta - "55253-0072-30" and "55253-0073-30" rather than "55523-0072-30" and "55523-0073-30"

Please let me know if you have any questions.

Thanks,
Kim

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

358 Page(s) 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/

SARA E STRADLEY
12/28/2011

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, December 21, 2011 1:46 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: RE: Patent certification

[Sorry about that.](#)

[The citation is](#)
21 CFR 314.50(i)(1)",

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

From: Lauren Wind [mailto:Lauren.Wind@weinberggroup.com]
Sent: Wednesday, December 21, 2011 1:32 PM
To: Stradley, Sara
Subject: RE: Patent certification

Dear Sara,

I understand the urgency of this request. To help be me better understand what the Agency needs, would you please confirm the reference to the CFR? I am unable to locate the section you cited.

Thanks,
Lauren

From: Stradley, Sara [mailto:Sara.Stradley@fda.hhs.gov]
Sent: Wednesday, December 21, 2011 1:05 PM
To: Lauren Wind
Subject: Patent certification

Hi Lauren

Please convey this to your team ASAP. We need this resolved as soon as possible.

Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 20-747 for Actiq (fentanyl citrate) transmucosal lozenge but does not contain a patent certification or statement

as described under 21 CFR 314.504(i)(1).

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/21/2011

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, December 21, 2011 1:05 PM
To: 'Lauren Wind'
Subject: Patent certification

Hi Lauren

Please convey this to your team ASAP. We need this resolved as soon as possible.

Your 505(b)(2) application relies upon the Agency's finding of safety and effectiveness for NDA 20-747 for Actiq (fentanyl citrate) transmucosal lozenge but does not contain a patent certification or statement as described under 21 CFR 314.504(i)(1).

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/21/2011

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, December 21, 2011 11:24 AM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Proposed language for Subsys

Hi Lauren

Below is proposed language (highlighted in blue) for the PI to address the mucositis issue:

(b) (4)

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/21/2011

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 15, 2011 2:11 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 15 Clinical IR #5

Hi Lauren

Please refer to the pending NDA 202788 for Subsys. We have the following information request. Please respond as soon as possible. Thanks

Also provide an integrated table of common adverse events, by preferred term for 05-001 and 06-007 with one table for all, one table for $\geq 5\%$, $\geq 2\%$ and $\geq 1\%$.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/15/2011

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 15, 2011 1:26 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 15 IR #4

Hi Lauren

Please refer to the pending NDA 202788 for Subsys. We have the following information request. Please respond as soon as possible. Thanks

Provide an integrated table of incidence of adverse events lead leading to discontinuation by preferred term for studies 05-001 and 06-007.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/15/2011

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 15, 2011 1:13 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 15 IR #3

Hi Lauren

Please refer to the pending NDA 202788 for Subsys. We have the following information request. Please respond as soon as possible. Thanks

Provide an integrated table of incidence of serious AEs by preferred term for studies 05-001 and 06-007.

The ISS reports 85 deaths, but the study reports for 05-001 and 06-007 report 3 and 89 deaths, respectively, why the discrepancy?

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/15/2011

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 15, 2011 11:16 AM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 15 IR #2

Attachments: Picture (Enhanced Metafile)

Hi Lauren

Please refer to the pending NDA 202788 for Subsys. We have the following information request. Please respond no later than Dec 20. Thanks

In listing 16.2.2, the following two protocol violations were not granted waivers

110006	19DEC2007	3	240.00	NO	EXPERIENCE PERSISTENT PAIN RELATED TO THE CANCER OR ITS TREATMENT	NO
110007	22JAN2008	3	102.00	NO	EXPERIENCE PERSISTENT PAIN RELATED TO THE CANCER OR ITS TREATMENT	NO

Why were these patients enrolled and included in the study?

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/15/2011

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, December 15, 2011 9:20 AM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 15 information request

Hi Lauren

Please refer to the pending NDA 202788 for Subsys. We have the following information request. Please respond no later than Dec 20. If you have any questions, let me know. If this information was submitted to the NDA already ,please provide the date of the submission. Thanks.

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 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.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/15/2011

Stradley, Sara

From: Stradley, Sara
Sent: Wednesday, December 14, 2011 3:39 PM
To: 'Lauren Wind'
Cc: Stradley, Sara
Subject: Dec 14 information request

Hi Lauren

Please refer to your pending NDA 202788 for Subsys. We have the following information requests. Please respond no later than Dec 20. If you have any questions, let me know.

The proposed Spray Content uniformity results for all strengths seem to indicate that the results are generally toward (b) (4) the proposed acceptance criteria. Take corrective actions to the manufacturing process to target the spray content to the proposed labeled claim (i.e., 100 % of labeled claim) for all strengths.

The specification proposed for Spray Actuation Content is not in accordance with the FDA guidance for Nasal Sprays. Tighten the proposed specification to be in agreement with the FDA guidance (e.g., individual sprays to within ± 15 percent of the target weight and their mean weight to within ± 10 percent of the target weight).

The pH range noted for some of the stability batches is wide with a maximum pH of (b) (4). Additional leachables can occur at pHs higher than (b) (4). Update the release and stability specifications to include testing for pH with data driven acceptance criterion.

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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

/s/

SARA E STRADLEY
12/14/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind"](#)
Subject: NDA 202788 - CMC IR
Date: Wednesday, November 09, 2011 1:16:00 PM

Hi Lauren,

Please refer to your pending NDA 202788 for Subsys. We have the following CMC IR (below). Please let me know if you have any questions.

Provide the Analytical method for HPLC determination of Spray Content Uniformity (PDR-ATM-IOX-0003).

Kind Regards,

Kathleen

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
12/14/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 - CMC IR
Date: Thursday, November 03, 2011 1:25:00 PM

Hi Lauren,

Please refer to your pending NDA 202788 for Subsys. The CMC review team has the following requests for information:

There is insufficient commercial scale product history, to support the lack of testing for both weight loss and ethanol assay during stability. Maintain both the ethanol assay test and the weight loss test during routine stability testing. Further, propose a release and stability specification for weight loss.

There is insufficient commercial scale product history, to support the complete (b) (4) proposed for stability testing. Include the first three production scale batches and a yearly production batch of the 4mg/ml intermediate strength in the stability protocol.

If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
11/09/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788
Date: Wednesday, September 28, 2011 2:20:00 PM

Hi Lauren,

Thanks for your update on the pending clinical IR and the recent submissions. The nonclinical team is reviewing the Ames results and has the following request:

Please submit the certificate of analysis for the drug substance (b) (4) (Lot# S813990) used in the Ames assay (Study # 158333) or direct us to its location in the submission.

Let me know if you have any questions.

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
11/09/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 - packaging
Date: Monday, October 03, 2011 4:57:00 PM

Hi Lauren,

Please refer to your pending NDA 202788 for Subsys and to your sample packages you sent to the Agency for review. Please clarify as to whether these are sample configurations and different materials will be used or if these are the packaging components that will be labeled and marketed. We are asking because your labeling calls your packaging child resistant so we want to understand if these are the packages that will be marketed as child resistant or whether different package materials will be used for market.

Please advise.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
11/09/2011

From: [Davies, Kathleen](#)
To: ["Lauren.Wind@weinberggroup.com"](mailto:Lauren.Wind@weinberggroup.com);
Subject: NDA 202788/request for information
Date: Friday, March 18, 2011 3:42:00 PM

Hi Ms. Wind,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We are conducting an initial review and cannot locate the following items (below). Please let us know where these are located in the NDA.

Kind Regards,

Kathleen

- 1. Please provide the location of the ISS.*
- 2. We note that in the study report for study INS-05-001, there does not appear to be a section 16 Appendices. This is usually where the protocol is placed (as was done for study INS-06-007, the safety study). Provide the location for the protocol and amendments for study INS-05-001.*

From: [Davies, Kathleen](#)
To: ["Lauren.Wind@weinberggroup.com"](mailto:Lauren.Wind@weinberggroup.com);
Subject: NDA 202788/fentanyl sublingual spray - request for information
Date: Friday, April 01, 2011 2:06:00 PM

Hi Ms. Wind,

Please refer to your NDA 202788 for fentanyl sublingual spray. We are currently reviewing the contents of your NDA and request the following information:

We note for your protocol INS-05-001 there were multiple amendments with revisions to the protocol. It is unclear from the submission what was modified with each protocol amendment. Please provide a summary of changes with each amendment and/or a track changes version of each protocol amendment, highlighting the changes. If there is a rationale for each change, please include that with each amendment.

If you have any questions, please let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: IR request_NDA 202788
Date: Monday, April 11, 2011 10:28:00 AM
Attachments: [IR_NDA202788.pdf.html](#)

Hi Lauren,

Please see attached clinical information request. Let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 - clinical information request
Date: Tuesday, May 03, 2011 12:53:00 PM
Attachments: [Clinical IR_202788.pdf.html](#)

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. The clinical team has the following requests for information/clarification (attached).

Please let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788/fentanyl sublingual spray - clinical IR
Date: Tuesday, April 26, 2011 12:38:00 PM

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We have the following requests for clarification (below). If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

- 1. In Table 14.1.1, one significant protocol violation is listed. Identify where this protocol violation is described.*
- 2. In Table 14.1.1, patient 108001 was discontinued from the study because of non-compliance under "other." Describe how this differs from a protocol violation.*
- 3. In 1.11.3 Information Amendment, Table I.B Information by Site there appeared to have been 161 patients "Screened," and in 1.11.3 Efficacy Information Amendment, Table 1: Disposition Flow Diagram for INS-05-001 there appeared to have been 160 patients "Screened." Clarify this discrepancy.*

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788/clinical information request
Date: Monday, May 23, 2011 10:56:00 AM

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We have a clinical request for information (below). Let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

-
- 1. Provide details on how patients were instructed in the use of the fentanyl sublingual spray during clinical studies.*
 - 2. Provide details on whether there was a supervision or observation period following the first dose of fentanyl sublingual spray.*
 - 3. Provide case report forms for all the patients that withdrew early from the trial because of "subject decision for withdrawal", "other", or "investigator decision."*

We have asked you to provide the location of protocol violation/deviation for patients in the Double-Blind Period and we were referred to Listing II.F in 1.11.3.1 Response to Division of Scientific Investigation Comments. However, this listing indicates "Protocol Violations/Deviations Titration Population (N=130)." Provide the location of protocol violation/deviation for

patients in the Double-Blind Period and confirm there were no early termination from the trial during the double-blind period.

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 - information request
Date: Thursday, September 01, 2011 2:29:00 PM

Hi Lauren,

Thank you for the update on the Ames test; I notified the pharmacology toxicology team of the update.

We have the following clinical question regarding your NDA:

In Listing 16.2.27, several patients with protocol deviations do not have a category assigned for any of the listed deviations, while others have more than one. Why are there patients listed with deviations without categorizations? Ex. Patient 105004 missed e-diary evaluations, and did not wait an appropriate length of time between pain episodes before treating another episode. Pt 105005 missed a diary assessment and dosed in error.

If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 clinical IR
Date: Wednesday, September 14, 2011 10:22:00 AM

Hi Lauren,

Please refer to pending NDA 202788 for fentanyl sublingual spray. We have the following clinical request for information:

- *The ISS does not include a discussion of the adverse event profile and its relationship to study drug, but appears to provide a series of embedded links to tables in brief paragraphs. Describe where your analysis of the safety of this product can be found. In addition, there is no mention of deaths in the text of the ISS, nor any links to narratives or related tables.*
- *Provide the location for narratives for all of the deaths in study 007. If not already provided in the NDA, submit within 7 days of receipt of this email.*

Please let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: RE: NDA 202788 clinical IR
Date: Thursday, September 15, 2011 3:43:00 PM

Hi Lauren,

See below. Let me know if you have further questions.

Kathleen

- *The ISS does not include a discussion of the adverse event profile and its relationship to study drug, but appears to provide a series of embedded links to tables in brief paragraphs. Describe where your analysis of the safety of this product can be found. In addition, there is no mention of deaths in the text of the ISS, nor any links to narratives or related tables.*

In the ISS, pages 19 (last paragraph) and 21 (conclusions) include a discussion of the adverse event profile and relationship to study drug. If this discussion is not sufficient, Insys would appreciate some additional guidance from the Agency on what information should be provided.

Division response: This is what is found on pages 19 through 21 (below). If this discussion is as in depth as you are able to generate, there is no need to repeat it. This is, however, very coarse and does not seem to do more than suggest the AEs were primarily due to underlying cancer.

AEs associated with study medication use or with mode of administration are shown in Table 14

(located in Appendix). Of 359 subjects in the safety population, 38.7% had events associated with medication use (e.g., sleepiness, dizziness, nausea, vomiting, confusion, hallucinations, weakness, shortness of breath, slow breathing, hypoventilation, slow heart

rate, low blood pressure, headache, itching, rash, abdominal pain, or occurrence of cold sores). Such events were seen with all Fentanyl SL Spray dose levels, with the greatest incidence (36%) in the subjects taking the highest dose (1600 mcg). Of the 359 subjects in the safety population, 11.1% had adverse events associated with mode of administration (e.g., sublingual erythema, edema or inflammation, or difficulty swallowing or eating). Such events were seen with all Fentanyl SL Spray dose levels though with the greatest incidence, 10.0%, in the subjects taking the highest dose (1600 mcg).

Laboratory results are presented for the Phase 3 studies INS-05-001 and INS-06-007 for hematology (See Table 15.1, located in Appendix), chemistry (See Table 15.2, located in Appendix), and urinalysis (See Table 15.3, located in Appendix). Data are presented at baseline, after 1 week of therapy, 1 month, 2 months, 3 months, 4 months, and at study end. Although some minimum and maximum values of specific lab tests were abnormal, mean and median values were unremarkable for all tests. Change from baseline values for hematology tests (See Table 16.1, located in Appendix), chemistry (See Table 16.2, located in Appendix) and urinalysis (See Table 16.3, located in Appendix) were unremarkable except for minor, clinically insignificant fluctuations over time in GGT. Baseline vs. final laboratory values for hematology (See Table 17.1, located in Appendix), chemistry (See Table 17.2, located in Appendix) and urinalysis (See Table 17.3, located in Appendix) were predominantly within limits. Rare telephone alert or panic values were noted for many hematology and

chemistry laboratories, generally including both increased and decreased values for any particular parameter. In general, this extent of laboratory alert abnormalities is considered expected for the patient population (cancer patients with breakthrough pain, with many underlying clinical conditions and many concomitant medications).

A summary of vital signs the Phase 3 studies INS-05-001 and INS-06-007 is presented in Table 18.1 (located in Appendix), and summary of change from baseline in Table 18.2 (located in Appendix). Minor fluctuations from baseline, after 1 week of therapy, 1 month, 2 months, 3 months, 4 months, and at study end were noted, but all appear usual for this population of cancer patients.

ECG results from Phase 3 studies INS-05-001 and INS-06-007 at baseline and at study end are presented in Table 19.1 (located in Appendix), and shift analysis in Table 19.2 (located in Appendix). At screening there were 4 (1.1%) clinically significant abnormal ECGs and 149 (42.2%) abnormal but clinically insignificant studies. These percentages were unchanged at study end. Only 3 studies showed a clinically significant shift from screening, 1 from normal and 2 from screening ECGs that were abnormal but clinically insignificant.

A broad range of concomitant medications from Phase 3 studies INS-05-001 and INS-06-007 is presented in Table 20 (located in Appendix). The concomitant medications are distributed across the Fentanyl SL Spray dose range. Common narcotic analgesics taken as concomitant medication (e.g., fentanyl, morphine, oxycodone, Vicodin and others) were

reported among approximately 20%-40% of subjects.

1.2. Conclusions from the Phase 3 Clinical Trials (INS-05-001 and INS-06-007)
The integrated safety database from INS-05-001 and INS-06-007 was 359 total subjects exposed to Fentanyl SL Spray. Exposures ranged from a minimum of only a few doses (if there was rapid drop-out in the treatment phases) to a long-term regular exposure (titration plus maintenance) that could include up to 3 months duration of chronic dosing in the open-label safety trial. The subjects evaluated in the integrated analysis of these 2 studies provided a diverse dataset of adverse events, with a total of 1921 events reported from 88% of the subjects in the safety database.

Given that all subjects in these studies were extremely ill with underlying cancer, the diverse adverse events profile and incidence of reported events are expected findings. Whereas some types of events, such as the common gastrointestinal and neurologic (e.g., somnolence and dizziness) events, are known side effects of fentanyl, others such as the common report of malignancy progression and cancer pain are clearly associated with the underlying disease.

Those events believed by the investigators to be likely associated with Fentanyl SL Spray were those known generally to be side effects of fentanyl. These events appeared to be dosedependent, as expected. No new toxicities related to Fentanyl SL Spray were identified.

Adverse events contraindicating further administration of Fentanyl SL Spray were not usually the cause of early termination from the studies, overall 22% of discontinuations in the safety

population. Of particular importance for the anticipated long-term use of Fentanyl SL Spray in patients living for long periods of time with cancer, chronic tolerability of Fentanyl SL Spray was high in the group of subjects treated for >3 months (49%, 175/359), of whom only 5 (2.9%) terminated due to adverse events.

In conclusion, the safety profile of Fentanyl SL Spray is adequate for its intended use in cancer breakthrough pain. The safety evaluation has not identified new toxicities not already expected

We confirm that there is no mention of deaths in the text of the ISS. However, information on the deaths that occurred in the studies can be found in 2.7.4 Summary of Clinical Safety in Section 2.1.2 Deaths as well as Appendix Table 18 Listing of Deaths. Does this information suffice? If not, Insys can develop an amendment to the ISS that contains a summary of the deaths that occurred in the studies, with reference to the relevant sections in 2.7.4 and the discussion of deaths in the CSRs (listings, tables, text).

Division Response: No. A complete ISS is required.

- *Provide the location for narratives for all of the deaths in study 007. If not already provided in the NDA, submit within 7 days of receipt of this email.*

There were a total of 89 deaths in INS-06-007. Only 1 of the deaths was determined to be possibly related to study drug, and consequently, only one narrative was prepared. This approach is consistent with the ICH E3 Guidance (p.30-31), which states that “Events that were clearly unrelated to the test drug/investigational product may be omitted or described very briefly.” Information on all deaths that occurred in INS-06-007 can be

found in INS-06-007 Listing 16.2.7.4 Listing of All Subjects Who Died and in 2.7.4 Appendix Table 18 Listing of Deaths.

Is the Agency requesting that Insys prepare narratives for the 88 subjects whose deaths were NOT related to study drug (i.e., deaths were related to progression of underlying cancer). If so, this effort will take more than 7 days to prepare. Would you please confirm if this is necessary? If so, I will need to confer with Insys as to how quickly this could be accomplished.

Division Response: *Yes, we are requesting narratives for the 88 deaths.*

From: [Davies, Kathleen](#)
To: ["Lauren Wind"](#);
Subject: NDA 202788 clinical IR follow up
Date: Friday, September 16, 2011 12:48:00 PM

Hi Lauren,

I spoke with Dr. Hertz and she provided the following advice based upon our conversation:

We do not accept investigator/sponsor reports that deaths are not attributable to study drug. We need to review the narratives so we can make a determination of relevance for each case. If you cannot accomplish this in 7 days, then as soon as possible.

We acknowledge you are not required to submit narratives, just CRFs for the deaths. However, if the data in the CRF is not sufficient to conclude that the death was not related to study drug, we will have to assume the death was related to study drug in our analysis. It is up to you to decide whether or not you want to submit narratives.

I hope this clarifies things a bit further for you. Please let me know if you still have additional questions.

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
11/09/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: RE: NDA 202788
Date: Monday, May 09, 2011 3:40:00 PM

Hi Lauren,

Please find the statistics information request in writing below. To confirm, yes, the 74-day letter will contain your PDUFA date and any additional information you may need about the review process. Once you receive the letter, if you have additional questions, let me know. You should receive it in the next 2 weeks.

Kind Regards,
Kathleen

Information Request for Study INS-05-001

1) Submit an additional dataset to facilitate ease of review. The data should include the following with multiple rows per patient:

- Pain intensity scores at each time point for each episode for each patient
- Pain intensity difference at each time point for each episode for each patient
- SPID30 for each episode for each patient. This should result in each patient having 10 SPID30 measurements.

Generate the same data for TOTPAR30.

2) To alleviate concerns regarding possible confounding of treatment with period effects, reanalyze the data using an ANCOVA model with fixed effects for treatment, period, sequence, and a random effect for patient. The dependent variable should be SPID30.

3) We additionally request that you conduct a re-randomization or permutation test. In general, the observed value of the test statistic is compared with values in a table of its theoretical distribution. When using a re-randomization test, you compare the observed value of the test statistic with the set of values obtained

by reassignments.

For your data, compute the test statistic from the original randomization using the model requested in 2. Reassign the observed data at random to 1 of the 29 sequences. Repeat until you obtain the distribution of the test statistic for all possible reassignments. Comparing the actual test statistic to this distribution then yields an exact p-value.

From: Lauren Wind [mailto:Lauren.Wind@weinberggroup.com]
Sent: Monday, May 09, 2011 2:32 PM
To: Davies, Kathleen
Subject: NDA 202788

Dear Kathleen,

Thank you for coordinating the call today (and I'm sorry about the phone issues!). Dr. Price's requests were very clear, and we look forward to receiving today's requests in writing. I have one additional question, and I apologize if this is ignorant. Will the Agency be issuing a PDUFA action date for NDA 202788, and if so, will that be in the 74-day letter? Or is it assumed that the action date is January 3, 2012 (unless there are other factors discovered during the review that lead to a delay in the action date)?

I appreciate your time today. We are working on responding to the clinical information request from last week as well as the new requests discussed today. If there are any issues in meeting the May 20th due date, I will let you know.

Best,
Lauren

Lauren H. Wind, MPH
Senior Consultant
The Weinberg Group Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036
P +1 202.730.4101
F +1 202.833.7057

weinberggroup.com

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

/s/

KATHLEEN M DAVIES
11/09/2011



NDA 202788

DISCIPLINE REVIEW LETTER

Insys Therapeutics, Inc.
(c/o) The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Lauren H. Wind, MPH
Senior Consultant
The Weinberg Group, Inc.

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated and received March 4, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Subsys (fentanyl sublingual spray).

The Division of Medication Error Prevention and Analysis completed their review of your submission, and have identified the following deficiencies:

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 must 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 must be re-tested in order to ensure safe use, especially in patients that are naïve to Subsys administration and use.
3. Prior to approval, the revised instructions must 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.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kathleen Davies, Senior Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SARA E STRADLEY
10/04/2011



NDA 202788

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Insys Therapeutics, Inc.
(c/o) The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Lauren H. Wind, MPH
Senior Consultant, The Weinberg Group, Inc.

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Subsys (fentanyl sublingual spray).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Kathleen Davies, Sr. Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Sara Stradley
Chief, Project Management Staff
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SARA E STRADLEY
09/07/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, August 11, 2011 4:18 PM
To: 'Lauren Wind'
Subject: Re: Information request - NDA 202788 8/11/2011

Dear Ms. Wind,

We are reviewing CMC section of your application NDA 202788 for fentanyl sublingual spray, and request following information:

- The specification limits shown in the batch analysis tables do not match with those proposed in the specification table and justification sections, 3.2.P.5.1 and 3.2.P.5.6. Clarify and submit the corrected BA tables.
- Confirm whether additional residual drug product can be sprayed after delivery of the single dose.
- Provide justification for the proposed limits of (b) (4), based on a toxicological risk assessment, since (b) (4) is not listed in ICH Q3C with a PDE.

Please acknowledge the receipt and provide a timeline for response.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
08/11/2011

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Monday, August 01, 2011 5:40 PM
To: 'lauren.wind@weinberggroup.com'
Subject: Re: NDA 202788 Information request

Dear Ms. Wind,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We have a Microbiology request for information as follows:

- **Provide descriptions of the test methods used for microbial limits. Also provide a summary of the microbiological method suitability testing with the drug product.**

Please acknowledge the receipt and provide tentative timeline for response. Let me know if you have any questions.

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

/s/

SWATI A PATWARDHAN
08/01/2011



NDA 202788

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Insys Therapeutics, Inc.
c/o The Weinberg Group, Inc.
1129 Twentieth Street, N.W. Suite 600
Washington, D.C. 20036

ATTENTION: Lauren H. Wind, M.P.H.
Senior Consultant

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated March 4, 2011, received March 4, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fentanyl Sublingual Spray, 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg.

We also refer to your March 14, 2011 correspondence, received March 14, 2011, requesting review of your proposed proprietary name, Subsys. We have completed our review of the proposed proprietary name, Subsys and have concluded that it is acceptable.

The proposed proprietary name, Subsys, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 14, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kathleen Davies at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
06/07/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788/clinical information request
Date: Monday, May 23, 2011 10:56:00 AM

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We have a clinical request for information (below). Let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

-
- 1. Provide details on how patients were instructed in the use of the fentanyl sublingual spray during clinical studies.*
 - 2. Provide details on whether there was a supervision or observation period following the first dose of fentanyl sublingual spray.*
 - 3. Provide case report forms for all the patients that withdrew early from the trial because of "subject decision for withdrawal", "other", or "investigator decision."*

We have asked you to provide the location of protocol violation/deviation for patients in the Double-Blind Period and we were referred to Listing II.F in 1.11.3.1 Response to Division of Scientific Investigation Comments. However, this listing indicates "Protocol Violations/Deviations Titration Population (N=130)." Provide the location of protocol violation/deviation for

patients in the Double-Blind Period and confirm there were no early termination from the trial during the double-blind period.

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

/s/

KATHLEEN M DAVIES
05/26/2011



NDA 202788

FILING COMMUNICATION

Insys Therapeutics, Inc.
(c/o) The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Lauren H. Wind, MPH
Senior Consultant
The Weinberg Group, Inc.

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated and received March 4, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for fentanyl sublingual spray.

We also refer to your submissions dated March 14, and April 5, 15, 21, and 29, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 4, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 16, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We also request that you submit the following information:

1. Provide results from exhaustive extraction studies of the activated (b) (4) HDPE bottle after addition of the maximum amount of drug product. These studies should include extraction with organic and inorganic solvents using ethanol, methanol, isopropanol, acetone, ethyl acetate, as well as water, at various time points (e.g., 1, 3, 6, and 12 hours), at room temperature and after heating and agitation. Provide similar studies under neutral, acidic and basic pH conditions at various time points.
2. Provide a photostability study for the drug product as per ICH Q1B.
3. To enhance patient comprehension, revise your proposed Medication Guide to target a 6th to 8th grade reading ease with a Flesch reading ease score of at least 60%. Your currently proposed Medication Guide has a grade level of 10.2 and a Flesch reading ease score of 50.2%. Refer to the currently approved Abstral Medication Guide as a template for your Medication Guide.
4. Provide the following items to your Risk Evaluation and Mitigation Strategy (REMS):
 - a. Dear Prescriber Letter;
 - b. Dear Inpatient Pharmacist Letter;
 - c. Dear Outpatient Pharmacist Letter;
 - d. REMS Overview – Prescriber;
 - e. REMS Overview – Outpatient pharmacy;
 - f. REMS Overview – Inpatient pharmacy;
 - g. REMS Overview – Patient/Caregiver; and
 - h. Distributor enrollment form.
5. To evaluate the abuse potential of your product, submit:
 - a. an analysis of abuse-related adverse events (AEs). This analysis should include all Phase 1, 2 and 3 clinical studies. For each clinical study, AEs should be categorized by dose and presented in tabular format;
 - b. a pooled analysis of abuse-related AEs. The pooled analysis should contain all abuse-related AEs, collapsed across studies, and categorized by dose;
 - c. information and data related to abuse, misuse, diversion and overdose. Specifically, submit descriptions of all reports and details, including narratives, of

an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies; and

- d. narratives and case report forms for patients that drop out from studies where they were enrolled for reasons that might be coded as "protocol violation," "lack of efficacy," "lost to follow up," "non-compliance to study medication or procedures," and "other."
6. Also, we note that in study INS-09-011, Subject #804 with Grade 2 mucositis has a C_{\max} value of fentanyl of 1.81 ng/mL and AUC_{last} value of 15.7844 ng/mL.hr. These values are significantly greater than those in patients without mucositis and with Grade 1 mucositis. This information may be included in the product label and used to provide a warning for patients with mucositis.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Kathleen Davies, Senior Regulatory Project Manager, at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

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

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

/s/

BOB A RAPPAPORT
05/11/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788 - clinical information request
Date: Tuesday, May 03, 2011 12:53:00 PM
Attachments: [Clinical IR_202788.pdf](#)

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. The clinical team has the following requests for information/clarification (attached).

Please let me know if you have any questions.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

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

/s/

KATHLEEN M DAVIES
05/03/2011

Davies, Kathleen

From: Davies, Kathleen
Sent: Tuesday, April 26, 2011 12:39 PM
To: 'Lauren Wind'
Subject: NDA 202788/fentanyl sublingual spray - clinical IR

Hi Lauren,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We have the following requests for clarification (below). If you have any questions, let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

-
- 1. In Table 14.1.1, one significant protocol violation is listed. Identify where this protocol violation is described.*
 - 2. In Table 14.1.1, patient 108001 was discontinued from the study because of non-compliance under "other." Describe how this differs from a protocol violation.*
 - 3. In 1.11.3 Information Amendment, Table I.B Information by Site there appeared to have been 161 patients "Screened," and in 1.11.3 Efficacy Information Amendment, Table 1: Disposition Flow Diagram for INS-05-001 there appeared to have been 160 patients "Screened." Clarify this discrepancy.*

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

/s/

KATHLEEN M DAVIES
04/26/2011

From: [Davies, Kathleen](#)
To: ["Lauren.Wind@weinberggroup.com";](mailto:Lauren.Wind@weinberggroup.com)
Subject: NDA 202788/fentanyl sublingual spray - request for information
Date: Friday, April 01, 2011 2:06:00 PM

Hi Ms. Wind,

Please refer to your NDA 202788 for fentanyl sublingual spray. We are currently reviewing the contents of your NDA and request the following information:

We note for your protocol INS-05-001 there were multiple amendments with revisions to the protocol. It is unclear from the submission what was modified with each protocol amendment. Please provide a summary of changes with each amendment and/or a track changes version of each protocol amendment, highlighting the changes. If there is a rationale for each change, please include that with each amendment.

If you have any questions, please let me know.

Kind Regards,

Kathleen Davies, MS

Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
(301) 796-2205 Office
(301) 796-9713 Fax

From: [Davies, Kathleen](#)
To: ["Lauren.Wind@weinberggroup.com";](mailto:Lauren.Wind@weinberggroup.com)
Subject: NDA 202788/request for information
Date: Friday, March 18, 2011 3:42:00 PM

Hi Ms. Wind,

Please refer to your pending NDA 202788 for fentanyl sublingual spray. We are conducting an initial review and cannot locate the following items (below). Please let us know where these are located in the NDA.

Kind Regards,

Kathleen

- 1. Please provide the location of the ISS.*
- 2. We note that in the study report for study INS-05-001, there does not appear to be a section 16 Appendices. This is usually where the protocol is placed (as was done for study INS-06-007, the safety study). Provide the location for the protocol and amendments for study INS-05-001.*

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

/s/

KATHLEEN M DAVIES
04/08/2011

From: [Davies, Kathleen](#)
To: ["Lauren Wind";](#)
Subject: NDA 202788/request for information
Date: Friday, April 08, 2011 11:06:00 AM

Hi Lauren,

Please see the following statistical information request below. If this information is already provided in the submission, please direct us to the location in the NDA.

Kind Regards,
Kathleen

*In Study INS-05-001, the primary efficacy endpoint is the time-weighted sum of pain intensity difference at 30 minutes (SPID30) following administration of study drug within a specific pain episode. You have provided datasets with summed SPID30 over breakthrough pain episodes treated with Fentanyl SL Spray and over episodes treated with placebo, as well as the difference between these two summed values for each subject. We have been unable to locate the data used to generate the primary efficacy endpoint, namely the pain intensity scores at 5, 10, 15, and 30 minutes per episode for each patient. Specify the location of this data within the submission. If the data has not been submitted, it should be provided no later than **April 15, 2011** along with data definition files with detailed information on how the variables are derived (i.e. formula) and which variables in the SDTM datasets are used in the calculation of the variables. If datasets (i.e. raw data) other than the SDTM datasets are needed to derive the variables, those datasets should also be submitted. Submit similar data for TOTPAR30 if it has not been submitted.*

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

/s/

KATHLEEN M DAVIES
04/08/2011



NDA 202788

NDA ACKNOWLEDGMENT

Insys Therapeutics, Inc.
(c/o) The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Lauren H. Wind, MPH
Senior Consultant
The Weinberg Group, Inc.

Dear Ms. Wind:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: fentanyl sublingual spray
Date of Application: March 4, 2011
Date of Receipt: March 4, 2011
Our Reference Number: NDA 202788

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 3, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2205.

Sincerely,

{See appended electronic signature page}

Kathleen Davies, M.S.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

KATHLEEN M DAVIES
03/17/2011



IND 072411

MEETING MINUTES

Insys Therapeutics, Inc.
c/o The Weinberg Group Inc.
1220 Nineteenth St, NW
Suite 300
Washington, DC 20036

Attention: Lauren H. Wind, M.P.H.

Dear Ms. Wind:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food Drug and Cosmetic Act for fentanyl sublingual spray.

We also refer to the meeting between representatives of Insys and the FDA on August 17, 2010. The purpose of the meeting was to discuss Insys's preparations for submission of an NDA for this product.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING**Meeting Date:** August 17, 2010**Time:** 1:30 PM EST**Location:** White Oak Conference Room 1315**Application:** IND 072411**Regulatory Status:** Active IND**Investigational Product:** fentanyl sublingual spray**Proposed Indication:** management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain**Sponsor:** Insys Therapeutics, Inc.**Type of Meeting:** Type B, PNDA**Meeting Chair:** Robert Shibuya, M.D., Clinical Team Leader

Division of Anesthesia and Analgesia Products (DAAP)

Minutes Recorder: Kimberly Compton, Senior Regulatory Project Manager, DAAP

Industry Representatives	Title
John N. Kapoor, Ph.D.	Chief Executive Officer, Insys Therapeutics, Inc.
Michael L. Babich	President & Chief Operating Officer, Insys Therapeutics, Inc.
Larry Dillaha, M.D.	Chief Medical Officer, Insys Therapeutics, Inc.
Venkat R. Goskonda, Ph.D.	Senior Director, Pharmaceutical Development, Insys Therapeutics, Inc.
Ashok J. Chavan, Ph.D.	Director of Pharmaceutical Operations, Insys Therapeutics, Inc.
Joel I. Falk	Executive Vice President, The Weinberg Group Inc.
Nicholas M. Fleischer, R.Ph., Ph.D.	Vice President, The Weinberg Group Inc.
Lauren H. Wind, M.P.H.	Consultant, The Weinberg Group Inc.
Teresa I. Henry, Ph.D.	Consultant to The Weinberg Group Inc.
Willene Brondum	Senior Manager of Regulatory Affairs, Insys Therapeutics, Inc.
Neha Parikh	Director of Clinical Operations, Insys Therapeutics, Inc.
FDA	Title
Bob A. Rappaport, M.D.	Director, DAAP
Sharon Hertz, M.D.	Deputy Director, DAAP
Luke Yip, M.D.	Medical Officer, DAAP
Robert Shibuya, M.D.	Medical Team Leader, DAAP
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer, DAAP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAAP
Danae Christodoulou, Ph.D.	CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Prasad Peri, Ph.D.	Acting Chief, Branch II, Division of PreMarketing Assessment 1, ONDQA
Srikanth Nallani, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Dionne Price, Ph.D.	Statistics Team Leader, Division of Biometrics II
Kate Meaker, M.S.	Statistical Reviewer, Division of Biometrics II
Kim Compton	Senior Regulatory Project Manager, DAAP
Kristina Toliver, Pharm.D.	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Gita Toyserkani, Pharm.D.	Team Leader, Division of Risk Management (DRISK), OSE
Stephen Sun, M.D.	Reviewer, DRISK, OSE

Agnes Plante, B.S.N.	Consumer Safety Officer, Office of Compliance
Jovita Randall Thompson, Ph.D.	Reviewer, Controlled Substance Staff (CSS)
Mike Klein, R.Ph., Ph.D.	Director, CSS

Background:

On August 12, 2010, (prior to the August 17 meeting) the Agency forwarded to the firm the Agency's comments and responses to the questions posed by the sponsor in their July 8, 2010, meeting package.

The firm indicated they would like to discuss Chemistry Questions 1, 3, 5, and 8, DMEPA Comments, Clinical Questions 4, and 5, and REMS Questions 1 and 2.

Presented below are the Agency's comments and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting is captured in normal text following the question to which it pertains.

Meeting:

The sponsor opened the meeting by stating that their company has one focus—the delivery of drugs through spray technology.

Chemistry Questions*Question 1*

Insys proposes to establish controls for the fentanyl drug substance based on standards recommended by the API manufacturer. Are the proposed tests and specifications for the drug substance adequate?

FDA Response

No, the proposed drug substance specifications are not adequate. The impurity (b) (4) contains a structural alert for mutagenicity and must therefore either be reduced to reflect NMT (b) (4) total daily intake or be adequately qualified for safety.

We remind you that drug substance specifications will be assessed during the NDA review as per ICH Q3A(R2) and the FDA draft Guidance: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*.

Discussion

The sponsor stated that they have spoken to their API supplier, and they are comfortable with the (b) (4) specification and so will commit to it. The Division stated that the (b) (4) limit was suitable provided that it was based on the maximum daily dose. The sponsor stated that they will ensure that the impurity (b) (4) will be reduced to (b) (4) and will be NMT (b) (4) mcg/day based on the maximum daily dose.

Question 2

Insys proposes to establish controls for the drug product as appropriate for an oral, sublingual dosage form. Are the proposed tests and specifications for the drug product (release and stability) adequate?

FDA Response

The proposed drug product specifications appear reasonable.

We remind you that drug product specifications will be assessed during the NDA review as per ICH Q3B(R2) and the FDA draft Guidance: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*.

Discussion

There was no further discussion on this point.

Question 3a

Insys intends to propose a shelf-life of 3 years for the drug product, based on long-term stability data. Do the drug product stability batch plan and testing protocol using a (b) (4) approach support the proposed expiry dating?

FDA Response

With respect to your stability plan, the proposed number of primary stability batches in Table 16, and extent of data to be submitted in the NDA is acceptable. However, the proposed stability protocol in Tables 17 and 18 is unclear and limited with respect to frequency of testing critical spray performance attributes, and is not acceptable.

You must demonstrate that critical product quality attributes, e.g., spray actuation content, spray content uniformity, droplet size distribution, and spray pattern are consistent and robust at all time points and orientations (b) (4) is not advisable.

Discussion

The sponsor referred to the handout they shared with the attendees at the meeting (a copy is appended at the end of this document following page 49.) The Division stated that since the product is a solution, (b) (4) is not an issue. In addition, the Division now understands that the product does not require priming, but noted that the sponsor will still need to demonstrate that the product dose delivery is consistent. The Agency is interested in trends in stability data, even if they are small, and large gaps in stability data are not acceptable based on ICH standards for testing intervals. The Division stated that the sponsor should provide all relevant development data for review in their NDA at the time of submission.

With respect to collecting data at different orientations, the sponsor stated (b) (4)

The Division requested that the sponsor provide data to support this claim. The sponsor stated that they could conduct some (b) (4) to better support the stability data.

The Division inquired if the NDA would contain 9, 12, and 18-month stability data and the sponsor stated that three batches are still aging and they plan to provide 12 and 18-month data. In order to see any trends, the Division requested data on all aspects of device performance and stability per ICH at the specified time points. (b) (4)

(b) (4) for the spray characteristics will require further internal discussion. The Division agreed to provide a definitive position on this issue as a Post-Meeting Note.

*****Post-Meeting Note—**

(b) (4), is not acceptable. Testing for all attributes, at minimum for the lowest and highest strengths, must be employed as per ICH recommendations for testing intervals, for your NDA batches. You may propose a “reduced testing” stability protocol, post-approval, after a complete assessment of the critical attributes of your product on stability, with sufficient supporting stability data in your NDA submission. Be advised, that insufficient stability data at the time of NDA submission, may put filing of your NDA at risk.

The Division observed that the sponsor’s stability program appears extremely complicated. (b) (4)

(b) (4) but the Agency still needs to see testing results at the time of NDA submission for review.

If the sponsor establishes that the proposed stability program is robust, then they may develop a protocol similar to what they are proposing for their more routine testing; however, ICH does not state that one may skip time points in primary stability protocols. The sponsor observed that ICH does provide for a reduced design option. The Division stated that in taking such an approach, the sponsor runs a risk that there may not be enough data to file/evaluate and provide a robust shelf-life for the product in the NDA.

Question 3b

Insys intends to propose a shelf-life of 3 years for the drug product, based on long-term stability data. Is the proposed format for stability data tables acceptable?

FDA Response

See response to Question 3a.

We remind you that expiration dating will be assessed during the NDA review, as per ICH Q1E, based on available real-time stability data and statistical analysis evaluation, as applicable.

Discussion

The Division stated that the stability table formats in Appendix 2 of the briefing document are acceptable.

Question 4

The NDA will include data on extractables and leachables from the drug product (b) (4). In addition, information will be provided by the spray device manufacturer to support the safety of (b) (4) components. Does the Division find that extractables and leachables from the (b) (4) have been adequately characterized?

FDA Response

Your approach to characterize extractables/leachables, i.e., include extractables information from the (b) (4) and a safety assessment of (b) (4) components in the NDA, appears reasonable.

We remind you that the adequacy of your studies to characterize extractables/leachables, will be assessed during the NDA review, based on available data.

Discussion

There was no further discussion on this point.

Question 5

The NDA will include data on drug product spray delivery after long-term storage during stability testing. In addition, Insys will submit data on spray delivery as a function of device orientation. Is the study of spray delivery as a function of device orientation adequate to demonstrate device functionality for bed-bound patients?

FDA Response

See response to Question 3a.

Your proposed stability protocol is insufficient with respect to testing spray delivery with device orientations. You must demonstrate that dose (spray) delivery, spray content uniformity, and spray pattern are consistent and robust in different orientations at all time points.

Discussion

The sponsor inquired whether the information provided on page 50 of the background package addressed the Agency's concerns regarding bed-bound patients. The Division stated that the sponsor will need to evaluate spray characteristics at all different device orientations. The sponsor's proposal is acceptable as long as the study is completed in accordance with the guidance for nasal sprays.

Question 6

In anticipation of commercial supply requirements, the spray device manufacturer will (b) (4). There are no changes in (b) (4) design from the (b) (4) employed for fabrication of clinical spray device parts. To qualify the commercial spray devices, Insys will manufacture process validation batches using spray devices assembled from parts fabricated with (b) (4). Does the Division agree with the proposed scale-up plan?

FDA Response

Yes, we agree.

Discussion

There was no further discussion on this point.

Question 7

Insys has developed a packaging/labeling scheme for the drug product incorporating color coding for dose differentiation, child resistant/senior accessible blister packaging and secondary package unit counts consistent with expected patient requirements. Does the Division find the proposed packaging/labeling approach suitable for this single-use sublingual spray?

FDA Response

The proposed packaging/labeling approach appears suitable for the single-use sublingual spray. The adequacy of the proposed packaging/labeling scheme will be assessed during the NDA review.

Clarify what you mean by color coding. Color “coding” generally refers to the use of color across product lines so that similar product strengths, active ingredients, or some other overlapping product characteristic utilize the same colors on labels and labeling (e.g. all oral transmucosal fentanyl (OTF) products using the same colors for corresponding strengths). If this type of color coding is what you are referring to we do not recommend the use of the same colors for the same strengths across OTF product lines.

However, if you are referring to color differentiation (i.e., the use of color to differentiate the product strengths within your fentanyl sublingual spray product line), the use of color can be an effective means for differentiating product strengths. A full review and evaluation of the labels, with color coding, will be done at the time of the NDA review.

Additionally, we note in section 7.2.6.9 of your briefing package, you state that each individual unit-dose system label will contain “at minimum, Product Name, Dose, Lot Number, Date of Expiry.” We recommend you also include the product strength on the label.

Discussion

There was no further discussion on this point.

Division of Medication Error Prevention and Analysis (DMEPA) Comments

- 1. If you have not already done so, a Failure Mode and Effects Analysis should be conducted to identify any failures that may be associated with this dosing device (e.g., wrong route of administration).**
- 2. Additionally, label comprehension studies should be conducted on any instructions for use.**

3. Clarify if it will be evident from the device that the dose has already been administered.

Discussion

The sponsor stated that they plan to complete a full FMEA as well as a labeling comprehension study, and to include information in the Medication Guide on how it will be evident that a dose has already been administered.

Question 8

The NDA will include data on residual API in the delivery device post-dosing. Are the data to be provided adequate to characterize the disposition of residual drug?

FDA Response

Your proposed disposal plan is not acceptable.

You have not discussed priming requirements for your product. Priming will impact the amount of residual drug at the end of use. Based on the gross estimate of your residual product, the residual drug amount(s) is unacceptable. Therefore, you must scientifically justify the lowest possible residual to assure performance of your drug product, and describe any modifications to the device material(s) and shape(s) of components, and drug load to minimize residual. Since this is a spray drug product and residual is inevitable, you must propose additional measures, e.g., use of a chemical or physical trap to eliminate residual, collection of used devices, and any other means of preventing the potential for abuse and misuse of your drug product. In addition, you must consider the environmental impact of the number of devices to be discarded and propose measures for collection and possible recycling of your devices.

We remind you that any possible modifications to your device must be implemented before commercialization, and adequately bridged by CMC data on device performance characteristics.

Discussion

The sponsor stated that each device is designed to have only one actuation. It does not need to be primed and cannot be fired again once actuated. The device has a (b) (4) residual volume after actuation (b) (4)

The Division stated that (b) (4)

(b) (4) This does not sound like a practical approach because it is just not likely to be completed on a regular basis. If the sponsor decides to propose such a step, they will need to provide data to show that it will actually occur in the home-use situation. The sponsor stated that (b) (4)

Question 9

Insys has developed a method for drug product disposal by patients after dosing or for unused product, to address concerns about potential accidental exposure, tampering or diversion. Does the Division find the proposed disposal approaches suitable?

FDA Response

As discussed above, your proposals for residual drug and device disposition are not acceptable. See response to Question 8.

Discussion

There was no further discussion on this point.

Additional Chemistry Comments

- 1. Clarify if priming studies have been performed, and if not, provide data to assess the delivered dose in your NDA submission.**
- 2. Provide a list of all manufacturing facilities, in alphabetical order, a statement about their cGMP status, and whether they are ready for inspections at the time of your NDA submission. For all manufacturing sites, provide a contact name with telephone and facsimile number at the site. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**
- 3. Provide letters of authorization to allow our review of all supporting master files for the NDA (e.g., drug substance and device manufacturer(s)).**

Discussion

There was no further discussion on this point.

Nonclinical Questions

Question 1

In the Nonclinical Overview section of the NDA, Insys intends to summarize the nonclinical information presented in the labeling and summary basis of approval documents for Actiq, Fentora® and Onsolis®. Insys will supplement this review with any new nonclinical literature on fentanyl published since the approval of Onsolis (July 16, 2009). Additionally, Insys will include information supporting the safety of drug product impurities and extractables and leachables from the dosing device. Insys will include tabular summaries of the impurity and extractable/leachable safety data and relevant new information present in the published literature if sufficient information is available. Does the Agency concur with this approach?

FDA Response

Yes, we agree. Your approach sounds acceptable. However, you must identify the product(s) that you intend to reference via the 505(b)(2) regulatory pathway. You cannot

rely on the Agency's Summary Basis of Approval to support the safety of a drug product but you may rely on the Agency's previous findings of safety and efficacy as represented by the referenced drug product label.

Discussion

There was no further discussion on this point.

Additional Nonclinical Comments

- 1. Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.**
- 2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry *Applications Covered by Section 505(b)(2)* available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>**

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

- 3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.**
- 4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance document, *Guidance for***

Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

As noted in the document cited above, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*” (emphasis added).

5. Any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

Adequate qualification would include:

- Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - Repeat dose toxicology of appropriate duration to support the proposed indication.
6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative *in vitro* bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled “Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.” Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.
 7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), you must include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.
 8. The NDA submission must contain complete and definitive safety information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled “Container Closure Systems for Packaging Human Drugs and Biologics.” The evaluation of extractables and leachables

from the drug container closure system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.. Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents *Container Closure Systems for Packaging Human Drugs and Biologics* and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*. Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at [http://www.pqri.org/pdfs/LE Recommendations to FDA 09-29-06.pdf](http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf).

9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment, may result in a Refusal-to-File or other adverse action.

Discussion

There was no further discussion on these points.

Clinical Questions

Question 1

No specific studies in patients with either renal or hepatic insufficiency have been conducted. It is the Sponsor's intention to use the same language used in the Actiq® label regarding these patients. Thus, the recommended language for this section would read as follows:



(b) (4)

Does the Agency agree?

FDA Response

You are not required to conduct specific studies in patients with renal or hepatic insufficiency with your product. However, we recommend that you conduct a literature search and propose new language if any new information is available at the time of your NDA submission. If no new PK information is available and if there is no new thinking on

the part of the Agency with respect to this class labeling type language, the same language present in the reference drug would be sufficient.

Discussion

There was no further discussion on this point.

Question 2

Because data on the efficacy of Fentanyl SL Spray derive from only one clinical study (INS-05-001),

(b) (4)

approach?

. Does the Agency agree with this

FDA Response

Your proposal is not acceptable. You will need to provide an integrated summary of effectiveness (ISE). Refer to the *Guidance for Industry- Integrated Summary of Effectiveness*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf> for the content of the ISE other than study data.

Discussion

There was no further discussion on this point.

Question 3

The objective of the Integrated Summary of Safety (ISS) is to assess the safety of Fentanyl SL Spray in opioid-treated subjects with breakthrough cancer pain. The safety parameters to be evaluated include adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiogram (ECG) results. Data from the four clinical pharmacology studies will be presented in the ISS as stand-alone in-text tables, along with the existing summaries from their respective clinical reports. Data from the two Phase 3 studies will be combined to present safety data in cancer subjects, on multiple doses of Fentanyl SL Spray, and over an extended period of time. The Statistical Analysis Plan (SAP) for the ISS, included in this briefing document in [Appendix 1](#), describes the combined analysis of INS-05-001 and INS-06-007. Insys believes that this SAP will provide the clinical data needed to adequately characterize the safety of Fentanyl SL Spray. Does the Agency concur?

FDA Response

Your proposed organization of the ISS appears acceptable. We expect the ISS to be a full integration of the trial results and any other information you are relying on for approval of the application. This integration should address how all the pieces together make up the application. You are expected to complete an integrated analysis which addresses how your product is linked to any item(s) you are referencing, how your product is relevant to any other information on which you are relying, and how you believe this represents a complete application package for your product.

Module 2 is intended to be a brief overview or summary and is limited in the amount of content. The ISS is intended to be located in Module 5.3.5.3.

You continue to refer to “opioid-treated” patients. That term is open to interpretation. This product is appropriate for opioid-tolerant patients as defined in labeling for similar oral transmucosal fentanyl products.

Discussion

There was no further discussion on this point.

Question 4

The Fentanyl SL Spray clinical development program, as discussed at the End-of-Phase-2 meeting, consists of three pharmacokinetic studies in healthy volunteers, one pharmacokinetic study in patients with or without mucositis, an efficacy and safety study in 130 patients, and a 3-month safety study in ≥ 150 patients (Refer to Section 5). Insys believes that these studies will be sufficient to form the basis of a determination of product safety and efficacy. Does the Agency concur?

FDA Response

Barring any unanticipated safety signals and presuming the results of your INS-05-001 trial are confirmed, we agree.

With respect to the pharmacokinetic (PK) study in patients with or without mucositis, we recommend that you include cancer patients with oral mucositis of grades 1, 2, 3, and 4. Alternatively, you may study cancer patients with grade 4 oral mucositis, and if there is no change in the PK in this group, patients with lower grade mucositis need not be studied.

Discussion

The Division stated that studies of the product in grade 4 mucositis patients are not feasible. Also, the product may be used in patients beyond only mild grade mucositis. Therefore, the sponsor should summarize the results of their studies to date and submit them for review. The Division will determine if additional study in this area is needed. If no effect is seen, the sponsor’s studies thus far may be sufficient, but if an effect is seen in mild mucositis patients, then more study will be needed. The sponsor agreed so submit an executive summary of their mucositis data.

Question 5

Given that all primary and secondary endpoints were achieved during the Insys placebo-controlled clinical efficacy study (INS-05-001) and particularly, [REDACTED] (b) (4)

[REDACTED] Does the Agency agree that such information, if supported by the clinical data, is suitable for inclusion in the label?

FDA Response

For the primary efficacy endpoint, a graphical representation of the data may be included in the label. [REDACTED] (b) (4)

For secondary efficacy endpoints, only clinically relevant information (assessed with appropriate outcome measures and analyzed with appropriate statistical methods) will be included in the label.

Discussion

The sponsor stated that [REDACTED] (b) (4)

REMS Questions

Question 1

Given the fluid nature regarding REMS for immediate-release opioids, when will the Agency be able to provide more guidance on this issue?

FDA Response

This product, as well as all transmucosal immediate-release fentanyl products, will require a Risk Evaluation and Mitigation Strategy (REMS).

A standardized type of REMS for these products is currently under Agency development and review; this information will be provided to you as soon as it is available. In the meantime, note that, at a minimum, your REMS will consist of the following elements: Medication Guide, Elements to Assure Safe Use, Implementation System and Timetable for Submission of Assessments.

Your REMS must also address proper disposal of residual fentanyl product in the device, prescribing to opioid-tolerant patients only, appropriate dosing of these fentanyl products, and surveillance for misuse and abuse.

You must submit a complete REMS at the time of initial NDA submission. Submit your REMS and REMS Supporting Document with your initial NDA submission as well as all planned materials identified within the proposed REMS that will be necessary to implement your proposal. Education should emphasize the safety messages important for safe use of the product. Product marketing materials generally are not appropriate to educate about product risks.

Discussion

The Division stated that the Agency is currently evaluating how an appropriate REMS for this class of product will look and plans to share this with all companies involved in development of products in this class; however, there is no specific timeline. It is possible this may still be unresolved at the time the sponsor submits their NDA. The Division stated that the sponsor may contact other companies that have products in this class and are working on REMS programs to see if they are willing to work together on a REMS. The Agency stated that a single system to include all products in the class is optimal, but each sponsor may need to first establish their own system as we move toward a shared REMS in the future. If there is any update on what the Agency feels is an appropriate classwide REMS by the time the minutes of the meeting are issued, it will be included as a Post-Meeting Note.

*****Post-Meeting Note—**

The Agency is facilitating a meeting to discuss REMS for the class of transmucosal, immediate-release fentanyl (TIRF) products on Oct 28, 2010. Insys has been invited.

The Division emphasized that the sponsor may find that working together with other companies toward a shared REMS may leverage firms that are not as willing to work on a shared REMS.

The sponsor stated that, rather than working with other companies for a shared system, they commit to the ETASU and Medication Guides already in place for other products in this class.

Question 2

Is the Agency considering a single, shared REMS program for immediate-release opioids?

FDA Response

We strongly recommend that you work with the other manufacturers of transmucosal immediate-release fentanyl products. In order to minimize the burden on the healthcare system and its various stakeholders, we recognize the importance of having one shared REMS system for all of these products, not just a REMS for an innovator and its generics.

Discussion

The Division stated that, while the Agency will continue to keep the sponsor updated on REMS requirements for this class of drugs, there have been situations where requirements have changed near the end of a review cycle delaying an action. If the NDA meets the minimum REMS requirements, it will certainly be fileable, but the Division is not certain how the class REMS will be implemented. The Division cannot guarantee that this application would not be caught in a period of change that would impact the Division's ability to approve the product and/or the sponsor's ability to market their product if approved. The Division is aware that, in particular, smaller companies seem receptive to working together to further this classwide REMS.

The Division does not want any risk to the patient, their family, or pets, which may occur if they are exposed to any product remaining in used or unused devices. The sponsor will need to address this in their REMS. In addition, the Division does not want the patient or family members taking the device apart and risking exposure. This is especially concerning if the exposed individual is a non-opioid-tolerant caregiver.

The abuse issue is separate but still needs to be addressed as well. The sponsor stated (b) (4) (u) (4) The Division suggested the sponsor focus on those aspects (b) (4) The Division stated that the sponsor will also need to address the issue of multiple bottles being in the home at the same time, as this lends itself to theft, while the residual product (b) (4) is a potential for accidental exposure. The Division suggested the sponsor consider employing a secondary packaging to keep track of what has been used and what remains. In addition, education of patients about proper storage is an essential element of the REMS. Any data the sponsor has to demonstrate that patients understand and will take steps to ensure proper storage will be helpful. The sponsor stated that they do have child-resistant blister packaging as part of their secondary packaging.

The Division stated that it is important to include in the NDA all work that has been done to demonstrate how difficult it is to recover any residual from the device. Such data helps support any statements in that area. Discussions of attempts people have made to abuse the product are typically part of any Advisory Committees on this topic, so the sponsor will need to know about them and be able to address them in their REMS. The sponsor should also be able to explain what will be done with unused units, since the product is used only as needed.

The Controlled Substance Staff (CSS) requested that data to support the sponsor's belief that (b) (4) in the class be submitted, as well as a proposal for proper storage of the product in the home. They directed the sponsor to formulate a proposal supported with data and submit it with the NDA.

The sponsor stated that they will (b) (4) The Agency instructed the sponsor to submit data to support that with their NDA, along with placebo-filled, final versions of the device.

The Division recommended that the firm consider secondary storage locations and issues, e.g., if the patient has several devices out at once in different locations, as well as data on what happens if the product is sprayed into other orifices (such as the nose) by accident. The Agency requested that the sponsor submit to the NDA any medication error data from the clinical trials as well. The sponsor agreed.

The Division stated that, at this time, formulation-specific disposal recommendations will be needed for the REMS because the products are different from one another and there is no single disposal method that can be applied to all. The sponsor does not need to explore every single method to reclaim the residual, but those that someone who is somewhat motivated might employ should be considered. There are experts in this field who could provide further input if needed.

CSS stated that they would be willing to review any proposals on this aspect of the product if the sponsor submits them. Their standard review time is approximately 30 days.

The Division stated that it is worth exploring (b) (4) The sponsor stated, however, (b) (4)

(b) (4)

*****Post-Meeting Note--**

An abuse potential study with your product, is not recommended. The abuse potential and safety of fentanyl is well known. Fentanyl is 80 to 100 times more potent than morphine. We have safety concerns with assessing this product in an abuse potential study. An abuse potential study measures the liking/euphoric effect of a drug and typically involves the administration of the drug at higher doses than the drug's therapeutic recommended doses. Also, the subject population in these studies, although experienced recreational users, are typically not tolerant to the respiratory depressant effects of the drug.

**At the meeting, you referred to the product as an (b) (4).
In your Pre-Meeting package there is reference to (b) (4).
(July 8, 2010 Pre-NDA (b) (4)
Meeting Briefing Package, page 44). Any claims made on (b) (4) or
any claims made on the relative safety of your product compared to any current
marketed fentanyl product would need to be supported with replicated data.**

In addition, we are particularly concerned about the possible use of the drug-device in commission of criminal acts because of the ease and rapidity of administering the drug either in a victim's mouth, or by inhalation, or in a drink. Fentanyl does not have an insignificant oral bioavailability. The victim could be rapidly overcome and, depending on the dose. This could result in serious morbidity or mortality. You need to address this concern and how such possible abuse or misuse of the product can be prevented.

You need to monitor drug use and accountability among subjects and monitor abuse-related adverse events in all future clinical studies with Fentanyl SL Spray. These data should be presented in tabular format in the NDA, when submitted.

Provide information on the expected number of dosage units of Fentanyl SL Spray that will be used per day for breakthrough pain. As with other transmucosal fentanyl products, in considering the patient population (opioid-tolerant patients), you do not propose a dose titration schedule for Fentanyl SL Spray, though as described, patients receive blister packs of 12 to 28 spray devices at one time when filling a prescription and are instructed to employ one dose, 1 or 2 spray devices as needed to attenuate breakthrough pain.

Division of Scientific Investigations (DSI) Comments

Comments I to III concern submission of data to the NDA that will be used for site selection and site inspection including information about potential use of electronic data capture of subject pain assessments for the primary endpoint. The Division of Scientific Investigations is piloting a "risk based site model" computer program, and the fourth item as well as the document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" relate to this pilot.

I. Request for general study related information as well as specific Clinical Investigator (CI) information to be used in site selection:

A. Please include the following information in a tabular format for the clinical trial:

- 1. Site number**
- 2. Primary investigator**
- 3. Location: City State, Country, including contact information (phone, fax, email)**

B. Please include the following information in a tabular format by site for the clinical trial:

- 1. Number of subjects screened at each site by site**
- 2. Number of subjects treated at each site by site**
- 3. Number of subjects treated who prematurely discontinued at each site by site**

C. Please include the following information in a tabular format for the clinical trial:

- 1. Name, address and contact information of all Contract Research Organizations (CROs) used in the conduct of the clinical trials**
- 2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies**
- 3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)**

D. Sample blank case report form

II. Request for Individual Patient Data Listings to be used for inspections:

For the trial INS-05-001 entitled “A Randomized, Double-Blind, Placebo-Controlled Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray (Fentanyl SL Spray) for the Treatment of Breakthrough Cancer Pain,” please submit site-specific individual subject data (“line”) listings from the datasets:

- A. Line listings for each site listing the subject number screened and reason for subjects who did not meet eligibility requirements**
- B. Line listings by site and subject, of treatment assignment and treatment administered. For this study, the listing for the treatment assignment refers to the 7 doses of active and 3 doses**

of placebo test article that were distributed to each subject during the double-blind period

- C. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason**
- D. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable**
- E. Line listings by site and subject, of AEs, SAEs, deaths and dates**
- F. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation**
- G. Line listings by site and subject, of the primary endpoint efficacy parameter, Summed Pain Intensity Difference at 30 minutes (SPID₃₀) and all of the pain values that were used to calculate this value (i.e. pain values from 0 to 30 minutes)**
- H. Line listings by site and subject, of the endpoint efficacy parameter, Summed Pain Intensity Difference at 60 minutes (SPID₆₀) and all of the pain values from after 30 minutes up to and including 60 minutes that were used to calculate this value**
- I. Line listings by site and by subject, of concomitant medications**

III. Additional request if electronic data capture of subject pain assessments (ediary) was used:

- A. Information concerning the electronic diary including instructions for use provided to subjects and investigators during the trial (Please include a description of support services available to subjects and investigators during the trial.)**
- B. Document the nature of the data generated by the electronic diary and describe the procedures used by the clinical investigator to collect and review the electronic diary**
- C. During the clinical trial, did sites retain the data in paper form or have access electronically? If electronic access, please describe**
- D. Data captured on the eCRFs and the eDiaries were provided to the CI on CD(s) at the close of the study (Please state who provided the CD(s) and the contents of the CD(s).)**
- E. Concerning the software:**
 - a. Who designed and developed the software?**
 - b. Could it be modified, or has it been modified? If so, by whom?**
 - c. Has the software been validated? Who validated the software?**
 - d. What was the process used to validate the software? How was the validation process documented?**

- e. **Were error logs maintained (for errors in software and systems) and do they identify corrections made?**
- f. **If data could be modified, how would the sponsor be aware of any changes?**

F. Concerning Data Flow:

- a. **Who was authorized to access the system and enter data or change data?**
- b. **Is there an audit trail to record changes to subject entries, including who, when, and why the change was made?**
- c. **Are there edit checks and data logic checks for acceptable ranges of values?**
- d. **How are the data transmitted from the subject to the sponsor or CRO?**

G. Concerning Computerized System Security:

- a. **How was system access managed, e.g., access privileges, authorization/deauthorization procedures, physical access controls? Are there records describing the names of authorized personnel, their titles, and a description of their access privileges?**
- b. **What methods were used to access computerized systems, e.g., identification code/password combinations, tokens, biometric signatures, electronic signatures, digital signatures?**
- c. **How were the data secured in case of disasters, e.g., power failure? Are there contingency plans and backup files?**
- d. **Were there controls in place to prevent, detect, and mitigate effects of computer viruses on study data and software?**
- e. **Were controls in place to prevent data from being altered, browsed, queried, or reported via external software applications that do not enter through the protective system software?**
- f. **When and how was data accessible to the clinical investigator?**

H. Were there written procedures for software validation, data collection, and computerized system security?

I. To facilitate our understanding of how data were transmitted from the eDiary and prepared for submission to the Agency, please provide a flow diagram that tracks the course of data generated by the subject through submission in the NDA. Please also include a diagram that tracks the course of the data to the clinical investigator for archiving at the end of the trial. The diagram should identify who was responsible for each step in the

process and should also specify points in dataflow where an audit trail exists.

IV. Request for Site Level Data for the risk based model

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide datasets, as outlined, for the study submitted in your application.

Discussion

There was no further discussion on this point.

Overall General Comment

Attachment 2 contains general comments on the content and format of an NDA submission and a Quality Assessment Tool.

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The sponsor understands that the impurity limit for (b) (4) of NMT (b) (4) is acceptable as long as the limit is based on the maximum daily dose and will be NMT (b) (4) mcg/day based on the maximum daily dose.
2. The sponsor clarified that the device does not need priming, and understands that they need to demonstrate that the device delivers a consistent spray over time, as well as fill in any missing gaps on the stability continuum.
3. The sponsor understands that it is important to evaluate dose delivery over time.
4. The sponsor understands that an abbreviated stability protocol may be acceptable, but only after fully establishing the stability protocol for NDA primary stability batches. The sponsor understands that they may follow this approach, but that it is at their own risk.
5. The issue of (b) (4) stability data at certain testing intervals being acceptable is to be addressed in a Post-Meeting Note (see page 5 of this document.)
6. The sponsor understands that demonstration of functionality in bed-bound patients is acceptable as long as they follow the guidance for nasal sprays.
7. The sponsor commits to conduct a FMEA and include that with the NDA. Data from this analysis may be useful for the Medication Guide.
8. The sponsor understands that the application will be filed if the minimum REMS requirements are addressed but that this is an area that remains under development within the Agency.

9. The sponsor understands that the Agency recommends they reach out to other firms with products in this class and consider working on REMS development cooperatively.
10. The sponsor understands there is a guidance on submission of proprietary names.

34 Page(s) 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/

KIMBERLY A COMPTON
10/18/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 72,411

Insys Therapeutics, Inc.
10220 S. 51st Street Suite 2
Phoenix, AZ 85044

Attention: Kelly D. Tate
Director, Regulatory Affairs

Dear Mr. Tate:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for your fentanyl sublingual spray product.

We also refer to the Type B, End-of-Phase 2 (EOP2) meeting between representatives of your firm and FDA on December 17, 2007. The purpose of the meeting was to provide you with feedback on the questions in your October 19, 2007 meeting package, which were specifically related to your preparations for undertaking Phase 3 studies with your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING RESPONSES



Meeting Date: December 17, 2007
Time: 1:00 PM EST
Location: White Oak Conference Room 1315
Application: IND 72,411
Regulatory Status: Active IND
Products: Fentanyl Sublingual Spray
Proposed Indication: The management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer.
Sponsor: Insys Therapeutics, Inc.
Type of Meeting: Type B- End-of-Phase 2 (EOP2)
Meeting Chair: Sharon Hertz, M.D., Deputy Director
 Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Minutes Recorder: Kimberly Compton, Project Manager, DAARP

Industry Representatives	Title
Kelly Tate, M.A., M.B.A., R.A.C.	Director, Regulatory Affairs, Insys Therapeutics, Inc.
Ellen Feigal, M.D.	Chief Medical Officer, Insys Therapeutics, Inc.
Ramesh Acharya, Ph.D.	Chief Scientific Officer, Insys Therapeutics, Inc.
(b) (4)	Consultant, (b) (4)
(b) (4)	Consultant, (b) (4)
FDA	Title
Bob Rappaport, M.D.	Director, DAARP
Yasmin Choudhry, M.D.	Medical Officer, DAARP
Mary Purucker, MD, Ph.D.	Medical Team Leader, DAARP
Elizabeth Bolan, Ph.D.	Pharmacology/Toxicology Reviewer, DAARP
Dan Mellon, Ph.D.	Supervisory Pharmacologist, DAARP
Kate Meaker, M.S.	Statistical Reviewer, Division of Biometrics II (DBII)
David Lee, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)
Prasad Peri, Ph.D.	Pharmaceutical Assessment Lead (PAL), Division of PreMarketing Assessment 1, Office of New Drug Quality Assessment (ONDQA)
Janice Weiner, J.D., M.P.H.	Regulatory Counsel, Office Of Regulatory Policy
Richard Abate, R.Ph., M.S.	Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Michael Klein, Ph.D.	Director (Acting), Controlled Substances Staff (CSS)
Silvia Calderon, Ph.D.	Team Leader, CSS
Kim Compton	Regulatory Project Manager, DAARP

Meeting Objective:

The purpose of the meeting was to provide the sponsor with feedback on questions from their October 19, 2007, meeting package, which were specifically related to the sponsor's preparations for undertaking Phase 3 studies with this product.

Background:

On December 14, 2007 (prior to the December 17, 2007 meeting) the Agency forwarded to the firm the comments and responses to the questions posed by the sponsor in their October 19, 2007, meeting package. The sponsor requested further discussion Questions 2 a and c, as well as portions of the Additional Regulatory Comments and CSS Comments were discussed at the meeting.

Presented below are the Agency comments related to the sponsor's background material and responses to questions in the background meeting package. The sponsor's questions are listed in *italics*, with Agency responses and comments in **bold**. Discussion that took place at the meeting follows in normal text.

Meeting:

Chemistry Questions

Question 4

Does the Agency concur that the drug delivery device for Fentanyl SL Spray is an oral delivery system and our proposed controls and testing of in process materials and finished products are adequate to demonstrate quality, strength, identity, purity and safety of products for filing an NDA under 505(b)(2)?

FDA Response

- 1. We concur that drug delivery device can be deemed an oral delivery system.**
- 2. We recommend consideration of the relevant portions of various CMC guidance documents ICH Q3A(R) and ICH Q3B(R), Container Closure Guidance, and Nasal Spray Guidance (links provided below) that may contribute to control of the drug product.**
- 3. Your proposed quality control strategy and attributes for the drug product listed in the specifications are a reasonable starting point, but please consider the following additional comments:**
 - a. All impurities in the drug substance and drug product should comply with ICH Q3A(R) (<http://www.fda.gov/cder/guidance/4164fnl.htm>) and ICH Q3B(R) guidance (<http://www.fda.gov/cder/guidance/7385fnl.htm>). Impurities that are deemed structural alerts need special consideration and should not exceed an exposure limit of NMT 1.5 mcg/day (see also, Nonclinical Comments). Acceptance criteria should be data-driven and will be evaluated during the NDA review.**
 - b. Due to the (b) (4) content of your drug product, you need to provide data addressing leachables in the drug product. Toxicological assessments will be necessary for the leachables.**

- c. **Provide a DMF for the spray pump and all other device components. Alternately, provide this CMC information in the NDA.**
- d. **Refer to the Agency's *Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics CHEMISTRY, MANUFACTURING, AND CONTROLS DOCUMENTATION* (<http://www.fda.gov/cder/guidance/1714fnl.htm>).**
- e. **In your NDA, provide justification for not testing the oral delivery system for all attributes as per the Agency's Nasal Spray guidance (<http://www.fda.gov/cder/guidance/4234fnl.htm>) e.g., weight loss (stability), droplet size distribution (including span) and percentage of droplets less than 10 microns, particulate matter, net content, leachables (stability), viscosity, and spray pattern.**
- f. **Define your drug product. For example, clarify how the device (vial and pump) will be assembled, provide appropriate patient instructions, and clarify if the vial and pump are co-packaged and/or foil pouched.**
- g. **Stability studies should be performed on the assembled device including the above parameters (mentioned in 3e above) unless justified.**
- h. **Provide the details (including validation) of the methods for the determination of the delivered dose, particularly respirable fraction and droplet size distribution.**

Discussion

There was no further discussion of this issue.

Chemistry Comments

1. **Include a well-documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.**
2. **At the beginning of the CMC section of your application, include a table of all facilities. Include specifically what the function of each facility is, the contact name and address, the CFN number, and the complete name and address of the facility.**
3. **Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming this in your NDA cover letter.**

4. Provide tabular summaries of your stability data, organized by test parameter and separated by manufacturing site, batch, storage condition and container closure system. Provide graphical summaries of any trending stability data, organized by test parameter, including mean and individual data.

Nonclinical Comments

1. You will need to provide complete characterization of leachables and extractables from the drug delivery system for the NDA.
2. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for the NDA submission (ICHQ3A(R), ICHQ3B(R)). Adequate qualification should include:
 - a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
3. The fentanyl drug substance may contain residual synthesis intermediates and/or impurities that contain structural alerts for mutagenicity such as: (b) (4)
A specification of NMT (b) (4) mcg/day should be set for genotoxic or potentially genotoxic residual intermediates/impurities. The Division recommends that you consult with your DMF holder to decrease the limit of these impurities. Adequate safety qualification for any potential genotoxic impurities should be provided with the NDA submission and should include:
 - a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies (point mutation assay and chromosomal aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
 - b. Repeat dose toxicology of appropriate duration to support the proposed indication.
 - c. Should this qualification produce positive or equivocal results, the impurity specification should be set at NMT (b) (4) mcg/day, or otherwise justified. Justification may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

Clinical Pharmacology Question

Question 1

Does the FDA concur that the human pharmacokinetic studies completed with Fentanyl SL Spray (absolute bioavailability, relative bioavailability compared to Actiq, ascending dose PK, and the effects of oral cavity pH and temperature on absorption rate and relative bioavailability) suffice as the pharmacokinetics package to support the submission of a 505(b)(2) application?

FDA Response

Yes

Discussion

There was no further discussion of this issue.

Statistical Questions

Question 2a

Insys proposes, as the main analysis method for the primary efficacy measure and related endpoints, using a repeated measures linear mixed model, and treating data at time points after the use of supplemental (“rescue”) medication as missing. Additionally we will perform sensitivity analyses, including those using imputation, to assess how conclusions about treatment effect depend on the handling of data after use of supplemental medication. Since we understand, in some instances, that the agency has adopted the baseline observation carried forward (BOCF) approach for such data, we will use BOCF to impute pain intensity at time points after the use of supplemental medication, and analyze the within-subject treatment summary using the Wilcoxon signed rank test. Does the agency agree with this statistical approach?

FDA Response

The Division’s concern regarding missing data has primarily been in the setting of parallel group, chronic pain trials. In such trials, patients receive treatment for 12 weeks. Patients may experience some reduction in pain intensity, however, they drop out of the study because of intolerable side effects. The Division has advocated using missing data strategies that assign a bad score to patients experiencing unfavorable outcomes.

You propose a crossover study design where patients assess pain intensity for 30 minutes following each treatment administration. The missing data concern is not the same as in the setting of parallel group chronic pain trials.

In general, a linear mixed model is an acceptable approach for analyzing the data. Your model will include fixed effects for treatment and time. The benefit of including an effect for time is unclear. Including terms for sequence and/or period may be more beneficial. Additional comments will be provided once the protocol and statistical analysis plan have been submitted.

Sponsor Reply (provided prior to Industry Meeting)

Insys noted FDA's comment that the "benefit of including an effect for time is unclear." Insys would like to clarify how the time effect is needed to identify the 30-minute time point of our main efficacy endpoint, As noted on p. 29 of the briefing document, the primary efficacy endpoint, i.e., the summed Page 7 IND 72,411 Insys Therapeutics Inc. EOP2 Meeting Minutes Fentanyl Sublingual Spray pain intensity differences at 30 minutes [SPID(30)], is defined mathematically as a linear combination of pain intensity (PI) at time points up and including 30 minutes.

Specifically:

$$SPID(30) = 30*PI(0) - 5*PI(5) - 5*PI(10) - 5*PI(15) - 15*PI(30).$$

However, rather than pre-calculating SPID(30) before statistical analysis, which might require imputation for missing data, we have chosen to implement the mathematical definition within the modeling and to allow the modeling to handle missing data automatically in the normal course of model fitting, without external imputation rules.

To see how this might work, consider an implementation of the mixed model using SAS, with PI as dependent variable and with the treatment (TRT) and time (TIME) factors as fixed effects. Suppose the levels of TRT are coded as 0 = Placebo and 1 = Fentanyl SL Spray, and the levels of TIME as 0, 5, 10, 15, 30, 45 and 60 (minutes). Given the model parameters and SPID as a function of PI, a statement in SAS to assess the treatment effect with respect to SPID(30) is:

```
Contrast "Trt effect SPID(30)" TRT*TIME -30 5 5 5 15 0 0 30 -5 -5  
-5 -15 0 0;
```

Insys noted the comment that "including terms for sequence and/or period may be beneficial." In the current analysis plan, the period effect is considered random, nested within subject. As a sensitivity analysis we will model period as a fixed effect, crossed with the subject effect. Also, there are 29 sequences, i.e., 29 different orderings of 3 placebo and 7 Fentanyl SL Spray treatments to which a subject may be randomized; we will examine the sequence effect descriptively.

Insys noted the comment that "additional comments will be provided once the protocol and statistical analysis plan have been submitted." Insys submitted the statistical analysis plan at the agency's request on December 5. If any questions or comments remain after our teleconference on December 17, Insys will look forward to hearing and discussing them.

Discussion

Ms. Meaker noted that the Agency's comment was related to the fact that linear models are often employed for longer study timepoints, so the Division was not sure these were the appropriate models to utilize. However, from the draft statistical analysis plan (SAP) the firm shared by email, she understands that the Agency will see both this analysis and the ANCOVA for the SPID (30) endpoint.

This is acceptable with the understanding that the Agency is interested first in the ANCOVA model results. Ms. Meaker stated that it is acceptable for the sponsor to conduct mixed-model imputation as a sensitivity analysis, noting that any discrepancies will need to be discussed in the study report.

The sponsor stated that they will amend their SAP based on the comments received and officially submit it to the IND.

Question 2b

In addition to citing the primary efficacy endpoint result, if it is statistically significant, Insys proposes to describe the time course of the treatment effect over the 60-minute breakthrough pain episode by graphing the Fentanyl SL Spray and placebo Pain Intensity Difference (PID) responses along with p-values at the different assessment times. Does the agency agree that if there are p-values < 0.05 the graph may be included in the package insert?

FDA Response

A graph may be included in the label if it is deemed clinically meaningful and relevant during the course of the review.

Discussion

There was no further discussion of this issue.

Question 2c

Provided that the statistical test of the primary endpoint is significant at level 0.05, Insys proposes to statistically test as secondary endpoints Total Pain Relief (TOTPAR) at 30 minutes and subject's Global Evaluation of Study Medication at 30 minutes. Each endpoint will be tested at the 0.05 level. Does the agency agree with this approach?

(b) (4)

FDA Response

Total pain relief at 30 minutes and subject's Global Evaluation of Study Medication may each be tested at the 0.05 level provided an appropriate statistical strategy for controlling the type I error is pre-specified.

Only clinically relevant information (assessed with appropriate statistical methods) will be included in the label.

(b) (4)

Sponsor Reply (provided prior to Industry Meeting)

Insys noted the comments that the secondary endpoints may be tested at the 0.05 level "provided an appropriate statistical strategy for controlling the type I error is pre-specified." One approach, consistent with the agency's comment, is to pre-specify one of the endpoints to be tested at the 0.05 level, with the other endpoint to be tested at the 0.05 level only if the first is statistically significant. We are also

considering an approach where both endpoints may be tested without prespecifying an order of testing. To control the overall false positive rate in this case, we propose to adjust the p-values from the two statistical tests using Hochberg's method (Hochberg, Y. (1988), "A Sharper Bonferroni Procedure for Multiple Significance Testing," Biometrika, 75, 800 - 803.) Does the agency concur that Hochberg's method is an appropriate statistical strategy for controlling the type I error?

Discussion

Ms. Meaker stated that the Hochberg method was appropriate. The sponsor stated that they had not yet decided how to address multiplicity. Ms. Meaker stated that it would be most important to pre-specify the plan to control for overall Type I error.

Statistical Comments

In Section 6, you request "concurrence on the statistical analysis plan for the Phase 3 pivotal trial." However, the meeting package does not include the protocol or statistical analysis plan for study INS-05-001. Statistical comments will be provided once the protocol and statistical analysis plan have been submitted.

Clinical Questions

Question 3a

Does the Agency concur that a 300 patient database of Fentanyl SL Spray, at doses ranging from 100 mcg to 1600 mcg, 150 of whom are patients who completed a three month safety trial, meets the requirements for the Agency's proposed safety database?

FDA Response

Assuming there are no unanticipated safety signals during the Phase 3 clinical trial or subsequently during the development program, a database of 300 patients is reasonable. This number should be comprised entirely of patients and not include normal subjects who have received the investigational product during pharmacokinetic studies. Out of this total number of patients, 150 should have been treated for a minimum of 3 months with investigational product that is reasonably representative of the proposed to-be-marketed doses.

Discussion

There was no further discussion of this issue.

Question 3b

From a clinical standpoint, does the Agency agree that the combination of completed studies along with the proposed studies underway constitute a filable 505 (b)(2) NDA?

FDA Response

A decision regarding the filability of your application will be based upon the application that is submitted and will include factors beyond the nominal clinical development program.

The results from a combination of completed and proposed clinical studies appear at this time to be reasonable to form the basis of a determination of product efficacy and safety. We remind you of your commitment to complete both a drug interaction study and a study conducted in patients with stomatitis.

Also see Additional Regulatory Comments below for further information on this topic.

Discussion

There was no further discussion of this issue.

Question 3c

[REDACTED] (b) (4)

Does the FDA agree with this request?

FDA Response

[REDACTED] (b) (4)

If the indication under study occurs in the pediatric population, the Pediatric Research Equity Act (PREA) requires you to study this product in pediatric patients.

We note that pursuant to the Food and Drug Administration Amendments Act of 2007 (FDAAA), a Pediatric Review Committee will be consulted on all pediatric plans and assessments prior to approval of an application or supplement for which a pediatric assessment is required as well as requests for deferral and waiver of pediatric studies. Therefore, the Division's comments on this issue should be considered preliminary.

Discussion

There was no further discussion of this issue.

Additional Regulatory Comments

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Sponsor Reply (provided prior to Industry Meeting)

Insys noted the FDA comment, "We remind you of your commitment to complete both a drug interaction study and a study conducted in patients with stomatitis." In the pre-IND meeting minutes from August 25, 2005, FDA commented that Insys should test the delivery system under clinical conditions that may potentially alter the absorption of the product, i.e., stomatitis or drug/drug interactions with other co-incident oral medications.

Insys did conduct pH and temperature testing in normal volunteers, and there was no impact on the pharmacokinetic profile of Fentanyl SL Spray. Insys is planning to examine the relationship between concomitant medications and adverse events, particularly serious adverse events, in the Phase III safety database. Insys is not planning additional drug-drug interaction studies (specifically, no pharmacokinetic studies are planned) with oral co-incident medications. Does the agency agree with this approach?

Insys will be studying this drug delivery system in a minimum of 20 patients with mild, moderate, or severe stomatitis. Insys will identify criteria for mild, moderate, and severe stomatitis, and evaluate safety in terms of local toxicity and systemic events. Insys is not planning a separate pharmacokinetic study in patients with stomatitis. Does the agency agree with this approach?

In the additional regulatory comments section, FDA refers to establishing a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. Insys has performed comparative bioavailability studies of Fentanyl SL Spray and Actiq; FDA has replied that these studies are sufficient for filing an NDA as part of the 505b2 strategy. The results of our study with Actiq were consistent with previously published data, and matches data in the public database. The results of our study with Fentanyl SL Spray revealed a bioavailability of 60.8%,

(b) (4)
[Redacted text block]

Does the agency agree with this approach?

Discussion

Dr. Lee stated that the Agency would need data on systemic blood levels of the product from 8-10 patients with mild stomatitis/mucositis in order to assess if membrane changes would lead to any changes in systemic absorption of the drug. Dr. Rappaport emphasized that this information would be required of the firm for this application. Dr. Lee stated that this data did not need to be collected in a separate PK study, but could be a subpopulation of a clinical study. He stated that the firm should collect blood samples to obtain C_{max} , T_{max} , concentration and characterize the elimination phase of the product.

Ms. Weiner stated that if the sponsor was planning

(b) (4)
[Redacted text block]

Office of Surveillance and Epidemiology (OSE) Comments

1. RISK MINIMIZATION ACTION PLAN—

- a. A complete review of the full risk management program (also referred to as Risk Minimization Action Plan or RiskMAP*) after the NDA is submitted will be necessary to determine whether the proposed program is acceptable, since additional information regarding risks and safe product use may emerge during ongoing clinical study. You should initiate a dialogue with the Agency regarding your RiskMAP development including a general discussion about the anticipated class-related risks such as abuse, diversion, overdose in patients, and accidental pediatric exposures.**
 - i. Submit your complete RiskMAP with the original NDA submission. Remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal (e.g., training materials, surveys, etc.)**
 - ii. We refer you to the following Guidance documents (available on the Agency’s website as listed below) for the most recent publicly available information on CDER’s views on RiskMAPs:**
 - Premarketing Risk Assessment:**
<http://www.fda.gov/cder/guidance/6357fnl.htm>
 - Development and Use of Risk Minimization Action Plans:**
<http://www.fda.gov/cder/guidance/6358fnl.htm>
 - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:**
<http://www.fda.gov/cder/guidance/6359OCC.htm>
- * We note that Title IX, Subtitle A of the Food and Drug Administration Amendments Act of 2007 (FDAAA) takes effect on March 25, 2008. The comments provided here with respect to RiskMAPs will be considered in the context of a Risk Evaluation and Mitigation Strategy (REMS) after that date. Information regarding submission of a proposed REMS will be forthcoming.**
- b. Submit any information on product medication errors or device failures from the premarketing clinical experience with the NDA application.**

2. PROPRIETARY NAME—

- a. It appears that the proprietary name you plan for this product is “Fentanyl SL Spray.” DMETS (a Division of CDER’s OSE that reviews**

proprietary names) has determined that this proprietary name is unacceptable because it may lead to medication errors.

- b. One concern is that “Fentanyl SL” may not clearly distinguish this product from the established names of other oral fentanyl products (e.g., Actiq, Fentora). Additionally, the use of the modifier “SL” in the proprietary name is unacceptable for several reasons:
- i. The letters “SL” are the common medical abbreviation for sublingual and could be confused solely as the route of administration rather than the modifier for the name resulting in another oral fentanyl product being administered sublingually.
 - ii. In addition, postmarketing surveillance shows that the SL modifier is prone to error and has been misinterpreted as “SC” and “XL.”
 - iii. Lastly, DMETS does not support the use of error-prone abbreviations in drug names or labeling because it contradicts the goals set forth for the Agency by healthcare practitioners and external medication safety organizations. In October 2005, FDA participated in a meeting sponsored by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) entitled “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk” and practicing health care practitioners at this meeting requested that FDA stop approving drug name modifiers that are ambiguous and error prone. Also, in June 2006, FDA launched a campaign in partnership with the Institute for Safe Medication Practices (ISMP) to warn health care providers and consumers not to use error-prone abbreviations.¹ To support this effort, DMETS recommends that these dangerous abbreviations not be utilized in labeling.
- c. Therefore, reconsider the use of the proprietary name “Fentanyl SL Spray” and propose an alternate name that uniquely identifies this product in the marketplace and avoids the use of error-prone abbreviations.

3. INDICATION FOR USE—

- a. (b) (4)
[REDACTED] However, this terminology is not consistent with other marketed fentanyl products (i.e.,
-

Actiq, Fentora) which use the term “opioid-tolerant.” Utilize the “opioid tolerant” terminology throughout your labeling materials.

- b. Clarify if you intend to implement any measures to prevent off label use.**

4. DOSING—

- a. Your Fentanyl SL Spray and Actiq do not appear to be bioequivalent. Therefore, the Agency is concerned that the Fentanyl SL Spray and Fentora are also not bioequivalent, though this information was not presented in the materials reviewed.**
- b. The fact that there may not be bioequivalence between the proposed Fentanyl SL Spray and the currently commercially available fentanyl products will increase the complexity of prescribing the oral fentanyl products and is a likely source of dosing error.**

5. OVERDOSAGE—

(b) (4) is not appropriate given that the product is predominantly SL absorbed.

6. PACKAGING—

- a. Submit the proposed device and all associated packaging (including the foil over wrap and study kit box), your plan of how to distinguish the different strengths of the product, your proprietary name and all associated labels and labeling as soon as possible as they are necessary for our review.**
- b. All warnings on the packaging should be consistent with the currently marketed Fentora brand of fentanyl.**

7. DEVICE—

- a. The Agency is concerned that, to a child, the device may resemble a toy. Clarify what child-resistance mechanisms will be utilized to prevent accidental exposure in children.**
- b. Clarify what feedback the patient will receive from the device to let them know the dose has been delivered.**
- c. Clarify if the product's overfill will be accessible after delivery (either as a partial second dose or through tampering with the device).**

- d. Clarify if it will be evident from the device that the dose has already been administered.
- e. Clarify how the different dosage strength will be differentiated.
- f. Clarify how this device will differ in appearance from a nasal inhaler.
- g. Clarify if the device can be taken apart.
- h. Clarify if usability studies have been completed for this device. If so, the Agency would be interested in reviewing the results.
- i. Clarify what you will recommend as the proper disposal method for the used device.
- j. Clarify if you have collected information on device failures in previous studies. Going forward with Phase 3 studies, the Agency recommends a prospective collection of device failures and patient complaints about the device.

8. ADMINISTRATION—

- a. Clarify the effect if the dose of this product is delivered to parts of the mouth other than underneath the tongue.
- b. As some cancer patients may be bed-bound and not able to sit upright, clarify if the orientation of the device might affect the delivery of the dose.

Discussion

There was no further discussion of this issue.

Controlled Substance Staff (CSS) Comments

1. As a Schedule II drug under the CSA, all Schedule II regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of study drug should be in place and strictly followed.
2. We are particularly concerned about the 30% of nominal dose of fentanyl that remains in the device following use. Describe how you will prevent diversion or abuse of the remaining active pharmaceutical product.
3. Preliminary PK review suggests that this product has enhanced bioavailability compared to currently available transmucosal fentanyl products as well as an increased C_{max} and decreased T_{max} when compared to the reference listed drug (RLD.) These same characteristics may influence the safety and the abuse and diversion potential of this product compared to other currently approved

formulations of fentanyl. You will need to address how abuse and diversion of this product can be limited, and develop appropriate plans for the disposal of the used product device. The safety concerns that have been identified with the use of other transmucosal fentanyl products will need to be addressed in this product's RMP.

- 4. Submit descriptions of all reports and details, including narratives, of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies.**
- 5. Provide narratives and case report forms for patients that drop out from studies where they were discontinued for reasons that might be coded as "protocol violation", "lack of efficacy", "lost to follow up", "non-compliance to study medication or procedures" or for "other."**

Sponsor Reply (provided prior to Industry Meeting)

The Controlled Substance Staff commented that the company should "provide narratives and case report forms for patients that drop out from studies where they were discontinued for reasons that might be coded as protocol violation, lack of efficacy, lost to follow up, noncompliance to study medication or procedures or for other." Insys notes that this would cover most of the non-safety reasons for early withdrawal. Would the FDA identify the specific issues or concerns they would like to ensure are included in the narratives?

Discussion of CSS Comments

Dr. Calderon stated that the Agency has concern about the incidence of diversion or any loss of product by theft, or other types of abuse of the product and wants these terms to be captured in the narratives. The Agency wants to get an idea of how the product behaves and, therefore, is requesting that the firm gather and submit all available information. Dr. Calderon agreed that a discussion of withdrawn patients in the narrative would be acceptable.

[REDACTED] (b) (4)

Dr. Rappaport strongly encouraged the sponsor to develop a plan to address the issue of child-resistance of units removed from the child-resistant blister, but not yet utilized. This plan should be included in the overall RiskMAP for the product. The sponsor indicated that they would develop such a plan and would contact CSS for assistance with it. All communication to the Agency should be through the Division project manager.

Dr. Rappaport pointed out that at the next milestone meeting for this product, the sponsor should have a very close to final RiskMAP developed. The sponsor inquired about a meeting to discuss the RiskMAP and Dr. Rappaport stated that due to our limited resources, the firm should submit their draft RiskMAP along with questions they have on it and the Agency will respond as soon as possible, but could not provide a timeframe for that response. He advised them to submit this material well in advance of the pre-NDA meeting. Dr. Rappaport stated that the firm should focus mainly on the content of the

four basic areas of the RiskMAP which potent opioids need to address: labeling, educational efforts for patients/prescribers/dispensers, surveillance for problems (especially those with accidental use or misuse), and intervention when signals do arise.

Closing Discussion

Regarding the Phase 3 protocol INS-05-001 entitled “A Randomized, Double-Blind, Placebo-Controlled Multi-Center Study to Evaluate the Safety and Efficacy of Fentanyl Sublingual Spray for the Treatment of Breakthrough Cancer Pain,” Dr. Purucker stated that substitution of the term “opioid-treated” in place of “opioid-tolerant” in the inclusion criteria of this trial was not acceptable. She stated that the firm should revert to the previous inclusion criteria language of “opioid-tolerant.” The sponsor agreed to make this change.

Dr. Purucker also stated that “fentanyl naïve” was an inconsistent and confusing term when used to describe eligibility criteria because it seemed to apply only to use of oral transmucosal fentanyl products and not to transdermal products. She requested that the sponsor clarify this in the protocol. The sponsor stated that they would clarify the term to “short-acting, commercially-available fentanyl.”

Dr. Peri stated that all stability studies should be performed on the final drug product. The firm stated this is what they were doing.

The sponsor summarized their understanding of the meeting as follows (includes action items)

1. The sponsor understands that the Agency will require further analyses if any discrepancies are seen in the first sensitivity analysis.
2. The description of the periods and sequences proposed seem acceptable to the Agency at this point.
3. The sponsor will amend their statistical analysis plan (SAP) based on the comments received and submit it to the IND.
4. The sponsor understands that the Hochberg method is an appropriate strategy and that the plan to control for overall Type I error must be prespecified.
5. The sponsor understands that the proposed pH and temperature are acceptable and that they do not need a separate study of concomitant medications. To address the stomatitis issue, the sponsor should examine the systemic blood levels in 8-10 patients with mild stomatitis. This can be accomplished as part of a clinical trial.

6.  (b) (4)

7. The sponsor understands that the Agency wants information on possible abuse, diversion, etc. captured and reported. This information should be reported in the narrative discussions.

Linked Applications

Sponsor Name

Drug Name

IND 72411

INSYS THERAPEUTICS
INC

FENTANYL SUBLINGUAL SPRAY

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

/s/

KIMBERLY A COMPTON

02/05/2008