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. EOPII 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:

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SPID(30) = 30*PI(0) – 5*PI(5) – 5*PI(10) – 5*PI(15) – 15*PI(30).
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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:

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

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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 signficant. 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
(b) (4)
Does the FDA agree with this request?

FDA Response
(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) *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)

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) **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.

(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/dipensers, 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. [redacted] (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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

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) 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) 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 [redacted] *In addition, information will be provided by the spray device manufacturer to support the safety of* [redacted] *components. Does the Division find that extractables and leachables from the* [redacted] *have been adequately characterized?*

FDA Response
Your approach to characterize extractables/leachables, i.e., include extractables information from the [redacted] **and a safety assessment of** [redacted] **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 [redacted] *. There are no changes in* [redacted] *design from the* [redacted] *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* [redacted] *. 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) 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 Gentoxicity 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.

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) *. Does the Agency agree with this approach?*

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, (b) (4) *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. (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 (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 classswide 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 [redacted]. The Division suggested the sponsor focus on those aspects [redacted]. 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 [redacted] 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 recovery 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 [redacted] 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 [redacted]. 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 [redacted]. The sponsor stated, however, [redacted]

[redacted] (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 then 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 [redacted] (b) (4).
In your Pre-Meeting package there is reference to [redacted] (b) (4) (July 8, 2010 Pre-NDA Meeting Briefing Package, page 44). Any claims made on [redacted] (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 ($SPID_{30}$) 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 ($SPID_{60}$) 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 [redacted] (b) (4) of NMT [redacted] (b) (4) is acceptable as long as the limit is based on the maximum daily dose and will be NMT [redacted] (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 [redacted] (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.

Attachment 1

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

FOLLOWING THIS PAGE, FDA_5408 TO FDA_5432 WITHHELD IN FULL AS B(4)/CCI

Fentanyl Sublingual Spray
Pre-NDA Meeting

August 17, 2010

CMC Question 3a
Clarification of Primary Stability Protocol Design

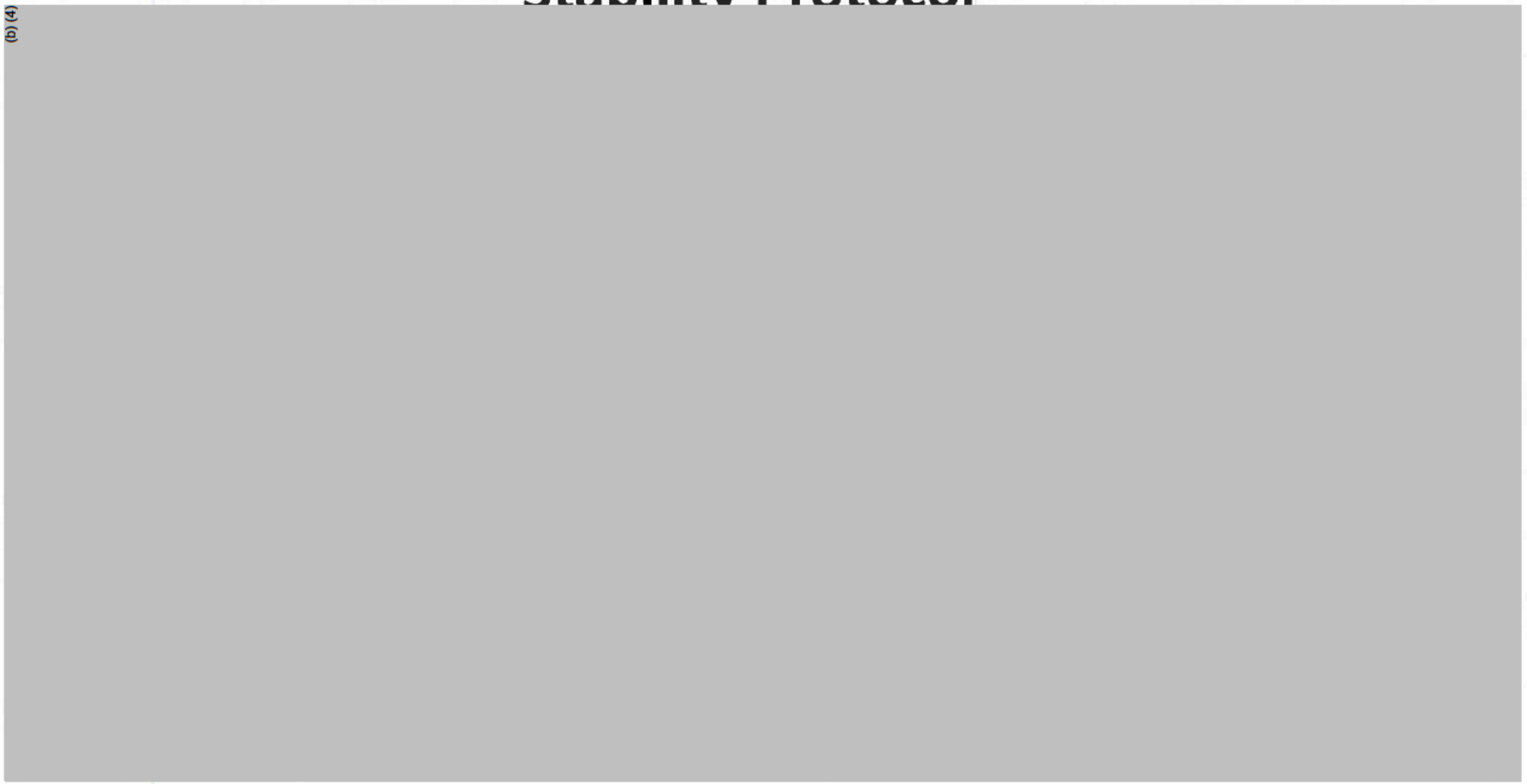
(b) (4)

Fentanyl Sublingual Spray Composition

(b) (4)

Fentanyl Sublingual Spray
Rationale for (b) (4) Design of Primary Stability Protocol

(b) (4)



Overview of Fentanyl Sublingual Spray Stability Protocol Design

(b) (4)

Fentanyl Sublingual Spray
NDA Stability Program
Spray Actuation Content, Spray Content Uniformity, Droplet Size Distribution, Spray Pattern

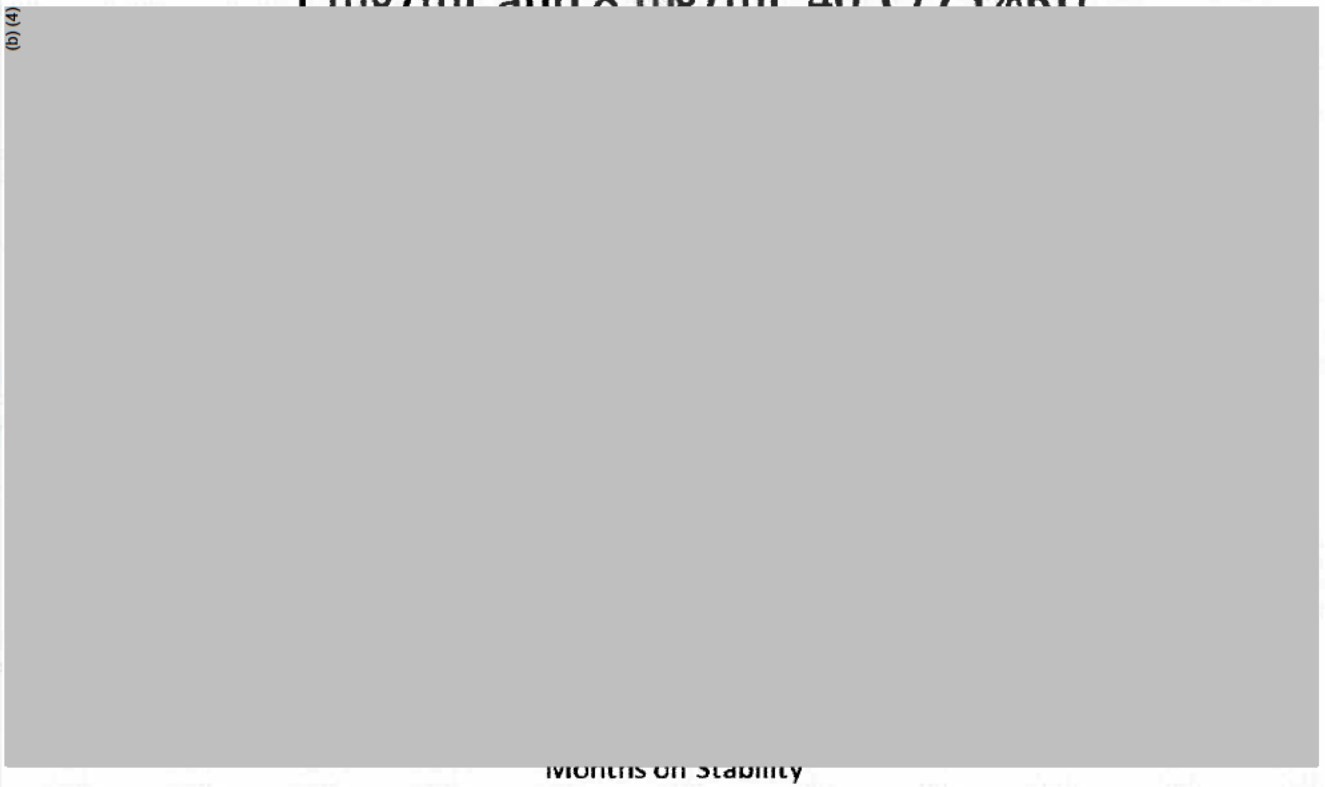
(b) (4)

Illustrative Stability Data

Spray Actuation Content

1 mg/mL and 8 mg/mL 40°C/75%RH

(b) (4)

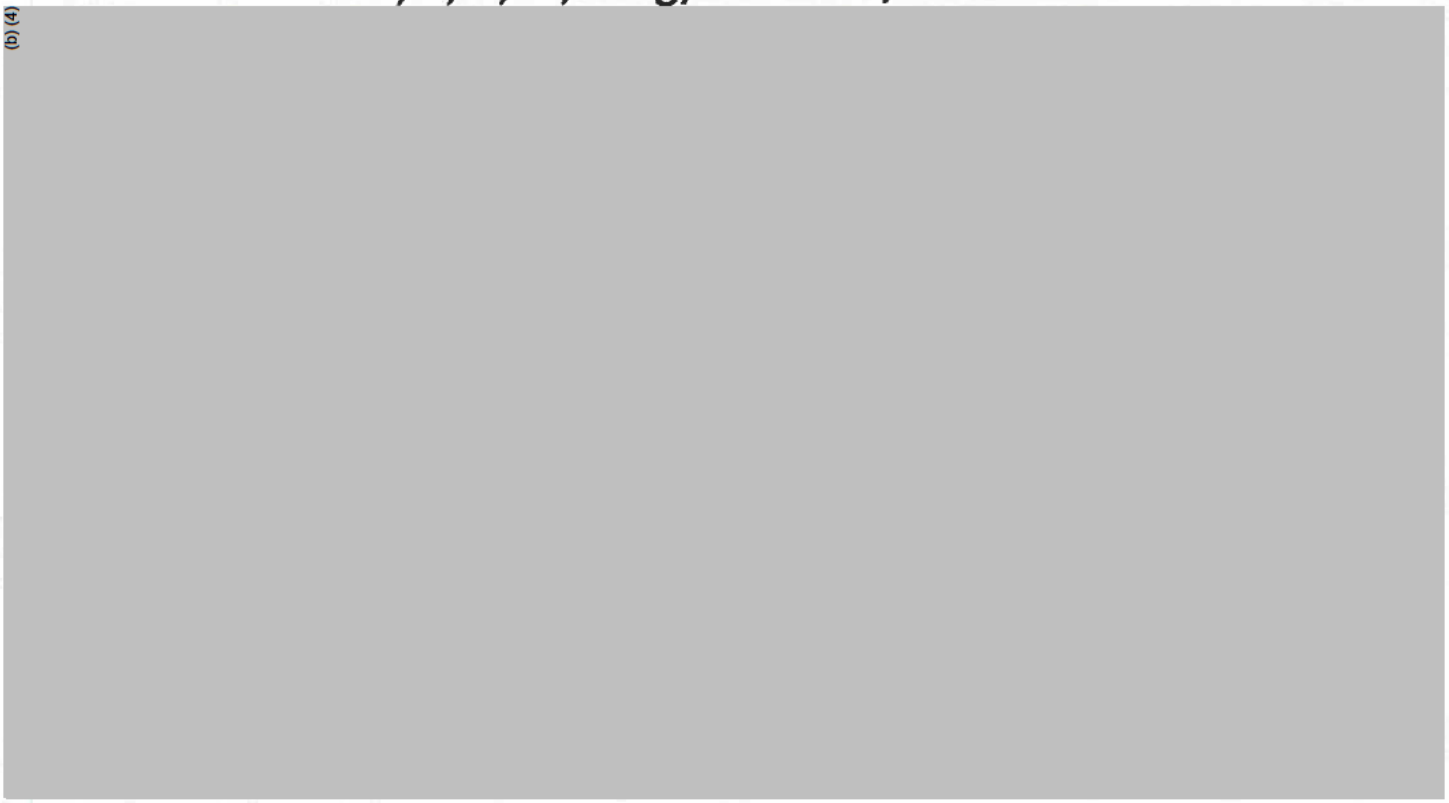


Months on Stability

Illustrative Stability Data

Spray Actuation Content
1, 2, 4, 6 ,8 mg/mL 25°C/60%RH

(b) (4)



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 AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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:	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

FOLLOWING THIS PAGE, FDA_5450 TO FDA_5807 WITHHELD IN FULL AS B(4)/CCI (PROPOSED/DRAFT REMS WEB MATERIALS)

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/s/

SARA E STRADLEY
12/28/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 29, 2011
To:	Bob Rappaport, M.D., Director Division of Anesthesia and Analgesia Products (DAAP)
Through:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead,** Doris Auth, Pharm.D., Risk Management Analyst **DRISK Review Team** Megan Moncur, M.S., Team Leader Gita A. Toyserkani, Pharm.D., MBA, Senior Risk Management Analyst
Subject:	Final Risk Evaluation and Mitigation Strategy (REMS) review for Subsys (Fentanyl) sublingual spray
Drug Name (Established Name):	Subsys, fentanyl citrate sublingual spray
Dosage and Route:	Sublingual spray 100mcg, 200mcg, 400mcg, 600mcg, and 800mcg
Therapeutic Class:	Opioid
Application Type/Number:	NDA 202-788
Applicant:	Insys Therapeutics, Inc

1. INTRODUCTION

The purpose of this review is to evaluate the proposed Risk Evaluation and Mitigation Strategy (REMS) for Subsys (Fentanyl) sublingual spray.

1.1 Product Overview

Subsys is a formulation of fentanyl, a potent opioid analgesic, for administration as a spray via the sublingual route, and a member of a group of Schedule II controlled substances that the Agency has collectively termed transmucosal immediate release fentanyl (TIRF) products. Actiq, Fentora, Onsolis, Abstral, and Lazanda are approved TIRF medicines indicated for the 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. These formulations deliver fentanyl rapidly via the oral mucosa in a variety of dosage forms. Drug delivery in this manner eliminates first pass metabolism that occurs with oral formulations and results in increased bioavailability. Subsys is the first of the transmucosal products to be delivered as a spray for sublingual administration.

The time to maximum concentration for Subsys varies with dosage, ranging from 0.67 hours for the 600mcg dose to 1.25 hours for the 100 and 200mcg doses. The proposed indication for Subsys the same as for the approved TIRF medicines.

The rate and maximum plasma concentrations vary considerably between the available TIRF medicines, as well as Subsys, therefore, they are not interchangeable. Life-threatening respiratory depression may occur at any dose in the following situations: in patients who are not opioid tolerant, if accidentally consumed by a child or for anyone for whom they were not prescribed, or if used for the treatment of acute or postoperative pain. It is because of these risks that a REMS is required for the transmucosal immediate-release fentanyl products.

1.2 Regulatory and Review History for Subsys and the TIRF REMS

Subsys has been part of ongoing and interrelated discussions within the Agency that included the review teams for other TIRF products, and often involved Senior Management. Following receipt of the Subsys NDA, Insys Therapeutics, Inc became a member of the TIRF REMS Industry Working Group (TRIG) and began collaborating with the group to align the Single-Shared System (SSS).

Following are highlights of key regulatory actions and communications regarding the REMS for Subsys as well as the TIRF REMS Single Shared System:

17 August 2010: Pre-NDA meeting, fentanyl sublingual spray (FSS), (IND 72-411, meeting minutes memo dated 10/18/10, Author: Compton, K) Insys was instructed to submit a REMS for FSS with their original NDA submission which must include a Medication Guide, Elements to Assure Safe Use, an Implementation System, and a Timetable for Assessments. The development of a Single Shared REMS for all manufacturers of TIRF products was discussed and Insys was encouraged to work with other manufacturers towards this goal.

28 October 2010: Meeting with all TIRF medicine sponsors (innovator and generic), to inform them that, in order to minimize the burden on healthcare providers and patients, a

single-shared REMS should be implemented for the TIRF medicines (Meeting Minutes: memo dated 01/03/2011; Author: Adeolu, Abolade A).

12 November 2010: REMS Notification letters were issued to all of the sponsors of the pending and approved TIRF products. The letters described the elements of the TIRF single-shared REMS that could be standardized and implemented for each TIRF product individualy, and ultimately across all TIRF medicines collectively, as a single-shared REMS.

04 March 2011: Subsys (NDA 202788; Seq No. 000) submitted. The original submission included a proposed REMS similar to the approved individual REMS for Abstral.

09 December 2011: Submission of the TIRF REMS SSS to the NDAs for Actiq, Fentora, Onsolis, Abstral, Lazanda, and to the ANDA for Fentanyl Citrate Oral Transmucosal Lozenge.

28 December 2011: Approval of the TIRF REMS Single Shared System for the above TIRF medicines.

- **28 December 2011: Submission of SUBSYS REMS (NDA 202-788, Sequence 028).**

2. MATERIALS REVIEWED

2.1 Data and Information Sources reviewed
Subsys Proposed REMS, submitted on December 28, 2011
Subsys Prescribing Information, original submitted on 3/4/11, revision December 28, 2011

2.2 Data and Information Sources referenced
DRISK Final REMS Review for the TIRF Products, Reviewer Toyserkani GA, dated December 27, 2011.

3. RESULTS OF REVIEW OF PROPOSED SUBSYS RISK EVALUATION AND MITIGATION STRATEGY

Insys submitted the proposed REMS for Subsys which is identical to the approved TIRF REMS SSS with the following exceptions:

- The Subys product name was added to the following documents:
    - All Letters (Dear Healthcare Provider, Inpatient and Outpatient Pharmacy, and Distributor)
    - Patient Prescriber Agreement
    - REMS Supporting Document
- Attachment 1 of the REMS (approved TIRF products) was also updated to include Subsys and is appended to the following documents:
    - All Overviews (Prescriber, Outpatient and Inpatient Pharmacy, Patient and Caregiver, Wholesaler)

- All Enrollment forms (Prescriber, Outpatient, Chain, and Inpatient Pharmacy, and Wholesaler/Distributor)

- Product specific information on Subsys was added to the Educational Program.

Please refer to the December 27, 2011 Final REMS Review which describes the REMS document and REMS appended materials and provides DRISK's concurrence with the single-shared REMS for the TIRF medicines.[1]

4. DISCUSSION AND RECOMMENDATIONS

The DRISK Review Team finds the proposed REMS for SUBSYS, as submitted December 28, 2011 (and appended to this review) to be acceptable, and recommends approval. Following approval of Subsys, each sponsor of an approved TIRF product in the SSS, will submit a proposed REMS modification which will be updated to include Subsys.

[1] Toyserkani G. Final REMS Review for Transmucosal Immediate-Release Fentanyl (TIRF) Products (NDAs 22-510, 20-747, 21-947, 22-569, 21-947, and 22-266), dated December 27, 2011.

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

/s/

DORIS A AUTH
12/29/2011

CLAUDIA B KARWOSKI
12/30/2011
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products

NDA/BLA #s:	202788
PRODUCTS:	Subsys (fentanyl sublingual spray)
APPLICANT:	Insys, Inc.
FROM:	Bob A. Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products
DATE:	January 2, 2011

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for fentanyl sublingual spray to ensure that the benefits of the drug outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. In reaching this determination we considered the following:

A. The estimated number of patients in the United States with breakthrough cancer pain is between 1 to 2 million. This estimate is based upon the number of patients with cancer in the US (American Cancer Society), the proportion of cancer patients with moderate to severe pain[1], and the proportion of cancer patients with breakthrough pain[2].

---

[1] Marieke HJ, van den Beuken-van Everdingen MHJ, deRijke JM, Kessels SG, Schouten HC, van Kleef M, Patijn. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. Pain 2007;132:312-320.

B. The patients for this product are cancer patients with pain that cannot be adequately controlled using around-the-clock oral or transdermal opioids alone. Many of these patients have multiple concurrent complications of their underlying disease and therapy.

C. The expected benefit of the drug to patients is that the delivery system is different from the existing oral transmucosal fentanyl products. This product is the first of these products to be formulated as a sublingual spray.

D. The expected duration of treatment with the drug will be from days for the sickest patients who are preterminal, to months for patients with less tumor burden and longer prognoses for survival.

E. The most serious of the known adverse events that are related to the use of fentanyl-containing products include death, respiratory depression, and CNS depression which occur primarily if the product is not used properly. In addition to the aforementioned risks, fentanyl sublingual spray, as other fentanyl-containing products, can have a potential to increase intracranial pressure and induce bradyarrythmias.

F. Fentanyl sublingual spray is not a new molecular entity

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Subsys (fentanyl sublingual spray). FDA has determined that Subsys (fentanyl sublingual spray) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Subsys (fentanyl sublingual spray). FDA has determined that Subsys (fentanyl sublingual spray) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks relative to benefits of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Subsys (fentanyl sublingual spray).

The elements of the REMS will be a Medication Guide, elements to assure safe use including prescribers training, pharmacies certification, and dispensing Subsys (fentanyl sublingual spray) to patients with evidence or other documentation of safe use conditions, an implementation system, and a timetable for submission of assessments of the REMS.

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

---

[2] Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;81:129-134.

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
01/02/2012

BOB A RAPPAPORT
01/03/2012

FOLLOWING THIS PAGE, FDA_5926 TO FDA_6135 WITHHELD IN FULL AS B(4)/CCI (PROPOSED/DRAFT REMS WEB MATERIALS)

February 8, 2012

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Addiction Products
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202788: SUBSYS (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0033: Amendment to the Approved REMS

Dear Dr. Rappaport:

Reference is made to Insys Therapeutics, Inc.'s New Drug Application 202788 for SUBSYS (Fentanyl Sublingual Spray) approved on January 4, 2012. Reference is also made to Kim Compton's email to Susan Franks of the TIRF REMS Industry Working Group dated February 1, 2012, which contained instructions regarding the language to use in this cover letter, as well as Kim Compton's email on December 22, 2011 regarding Risk Evaluation and Mitigation Strategy (REMS) documentation.

The SUBSYS REMS was approved on January 4, 2012 as part of the single, shared REMS system developed for the transmucosal immediate-release fentanyl (TIRF) class of products. The REMS system has not been implemented yet and at this time, no data are available to generate an assessment report.

This submission contains the following aggregate files:

- REMS and Materials
- Supporting Document

This submission also contains the following individual files:

- REMS
- Prescriber Overview
- Education Program
- Knowledge Assessment
- Prescriber Enrollment Form
- PPAF
- Patient and Caregiver Overview
- FAQ
- Website
- HCP Letter
- Outpatient Pharmacy Overview
- Chain Pharmacy Overview
- Inpatient Pharmacy Overview

- Outpatient Pharmacy Enrollment Form
- Chain Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Letter
- Inpatient Pharmacy Letter
- Distributor Letter
- Distributor Enrollment Form
- Supporting Document_Word

Should you have any questions or require additional information, please contact me by phone at +1 202.730.4101, facsimile at 202.833.7057, or email at lauren.wind@weinberggroup.com.

Very truly yours,

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

LHW/lw

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Symantec Endpoint Protection
Program Version	11.0.5002.333
Virus Definition Date	2/8/2012 rev. 4
Submission Size	Approx. 26 MB

The IT point of contact for this submission is:

Name	Lauren Wind
Phone Number	202-730-4101
Email Address	Lauren.Wind@weinberggroup.com

September 25, 2012

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Addiction Products
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202788: SUBSYS™ (fentanyl sublingual spray) for the management of breakthrough cancer pain
Sequence No. 0041: TIRF REMS Modification #2

Dear Dr. Rappaport:

Reference is made to Insys Therapeutics, Inc.'s New Drug Application 202788 for SUBSYS (fentanyl sublingual spray) approved on January 4, 2012. Reference is also made to Mark Liberatore's e-mail dated June 28, 2012 in which he provided an overview of the additional changes needed to incorporate closed system pharmacies into the TIRF REMS Access Program for pre-submission review by Wednesday, July 25, 2012. The following files were transmitted to Mark Liberatore via email on July 24, 2012, but FDA requested that this information be formally submitted to the NDA.

In response to this request, the following revised files are provided in this sequence:

- Chain Pharmacy Enrollment Form
- Closed System Pharmacy Overview
- Education Program
- FAQ
- Outpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Letter
- REMS (Please note: There is one difference from the previous submission made in July. In Section III a reference "ANDA" Sponsors was added.)
- TIRF Supporting Document

Should you have any questions or require additional information, please contact me by phone at +1 202.730.4101, facsimile at 202.833.7057, or email at lauren.wind@weinberggroup.com.

Very truly yours,

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

LHW/lw

Electronic Submission Specifications

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Anti-Virus Program	Symantec Endpoint Protection
Program Version	11.0.5002.333
Virus Definition Date	9/23/2012 rev. 8
Submission Size	Approx. 1.5 MB

The IT point of contact for this submission is:

Name	Lauren Wind
Phone Number	202-730-4101
Email Address	Lauren.Wind@weinberggroup.com

May 20, 2014

Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Addiction Products
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202788: SUBSYS® (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0081: Reference to REMS Modification (#3) filed to TIRF REMS DMF #027320

Dear Dr. Rappaport:

Reference is made to Insys Therapeutics, Inc.'s New Drug Application 202788 for SUBSYS (Fentanyl Sublingual Spray) approved on January 4, 2012. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 which contains the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products submitted to this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF," Insys hereby notifies FDA of its submission of Modification #3 to the TIRF REMS DMF #027320 in Sequence 0009 on May 20, 2014. The modifications are comprised of changes requested by the FDA in an e-mail dated February 5, 2014, and further changes proposed by the TIRF REMS Industry Group ("TRIG") on March 24, 2014 which were subsequently authorized by FDA on April 22, 2014.

There have been no post approval clinical trials completed or ongoing during this reporting period.

Please note that the 24 Month REMS Assessment for the TIRF REMS Access Program was previously submitted on December 27, 2013 in Sequence 0007 to DMF #027320.

Should you have questions or require additional information, please contact me by telephone at 602-910-2617 Ext. 9022, facsimile at 602-910-2627, or e-mail at wbrondum@insysrx.com.

Sincerely,

Willene M. Brondum
Director, Regulatory Affairs

WMB/wb

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	05/17/2014 rev. 1
Submission Size	Approx. 2.85 MB

The IT point of contact for this submission is:

Name	Willene Brondum
Phone Number	602.910.2617 ext. 9022
Email Address	wbrondum@insysrx.com

November 26, 2014

Sharon Hertz, MD
Acting Director, Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202788: SUBSYS® (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0090: Reference to Amendment to Prior Approval Supplement TRIF REMS Modification #3 Filed to TIRF REMS DMF #027320

Dear Dr. Hertz:

Reference is made to Insys Therapeutics, Inc.'s New Drug Application 202788 for SUBSYS (Fentanyl Sublingual Spray) approved on January 4, 2012. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 which contains the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products submitted to this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Insys hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in sequence 0012 [November 25, 2014].

The modifications to the TIRF REMS program included in this submission are comprised of changes requested by the FDA in e-mails dated October 20th, November 6th, and November 18th, 2014 and furthermore, consist of changes proposed and accepted by the TIRF REMS Industry Group ("TRIG") and FDA, respectively on November 7th, 2014. All updated TIRF REMS documents are submitted as both red-lined and clean versions in MS Word format. In addition, PDF documents of the RSD with Appendices and REMS with Supporting Materials are provided. Please note that unchanged TIRF REMS documents are not being resubmitted, but are referenced in the Reviewer's Guide and hyperlinked to the current version. All changes to the TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a MS Word file with screenprints in the clean versions.

Should you have questions or require additional information, please contact me by telephone at 480-500-3150, facsimile at 602-910-2627, or e-mail at vgoskonda@insysrx.com.

Sincerely,

Venkat Goskonda
Vice President, Research and Development / Regulatory Affairs

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	11/20/2014 rev. 3
Submission Size	Approx. 2.90 MB

The IT point of contact for this submission is:

Name	Elena Renaud
Phone Number	(480) 500-3166
Email Address	erenaud@insysrx.com

December 11, 2014

Sharon Hertz, MD
Acting Director, Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202788: SUBSYS® (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0092: Reference to Amendment to Prior Approval Supplement TRIF REMS Modification #3 Filed to TIRF REMS DMF #027320

Dear Dr. Hertz:

Reference is made to Insys Therapeutics, Inc.'s New Drug Application 202788 for SUBSYS (Fentanyl Sublingual Spray) approved on January 4, 2012. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 which contains the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products submitted to this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in sequence 0013 [December 10, 2014]. Prior amendments to the REMS for Modification #3 were submitted on April 1, 2014, May 21, 2014 and November 25, 2014. (The last REMS Assessment for the TIRF REMS Access Program was submitted on December 27, 2013.). Also, enclosed for the reference is the medication guide for SUBSYS (Fentanyl Sublingual Spray).

In conjunction with the correspondence received November 26, 2014 from Vaishali Jarral of your office, provided herein is the complete documentation of the TIRF REMS Access program including the requested "Dear" letters which were previously omitted. Please note that for the ease of review, this submission (DMF Sequence # 0013) contains the updated TIFR REMS documents in both red-lined and clean versions in MS Word format that were previously submitted via Sequence 0012 on November 25, 2014. All documents are referenced in the Reviewer's Guide and hyperlinked to their current version. All changes to the TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a MS Word file with screenprints in the clean versions. No new changes requiring additional FDA review are proposed at this time.

Should you have questions or require additional information, please contact me by telephone at 480-500-3150, facsimile at 602-910-2627, or e-mail at ssherman@insysrx.com.

Sincerely,

Stephen W Sherman

Stephen Sherman
Vice President, Regulatory Affairs

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	12/09/2014 rev. 4
Submission Size	Approx. 3.5 MB

The IT point of contact for this submission is:

Name	Elena Renaud
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June 12, 2017

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

NEW SUPPLEMENT FOR NDA 202788/S-0128
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT S-016

RE: NDA 202788: SUBSYS® (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0128: PRIOR APPROVAL SUPPLEMENT - PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES (S-018)

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011, for Insys Development Company, Inc.'s SUBSYS® (Fentanyl Sublingual Spray), which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013. Reference is also made to the REMS Modification Notification letter received on April 10, 2017.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Insys hereby notifies FDA of submission of the REMS modification, to update the REMS materials with the recent safety label changes as requested by the FDA in the REMS Modification Notification letter, to the DMF #027320 in eCTD sequence 0029 on June 09, 2017. As requested by the Agency, the proposed modified REMS and other REMS-related materials were submitted in Microsoft Word format.

In addition to the above REMS modification, as proposed in the response to the 60-Month Assessment Report Information Request 1 by the TRIG, the proposed Dear Healthcare Provider Letter is submitted to the DMF eCTD in Sequence 0030 on June 09, 2017. The Dear Healthcare Provider Letter is provided in a separate sequence as a stand-alone submission to clarify it as a one-time (single-use) communication rather than a new document being appended into the REMS itself.

If you have any questions regarding this submission, please contact me by telephone at (480) 500-3150 or by email at ssherman@insysrx.com.

Sincerely,

Stephen W Sherman

Stephen Sherman
Sr. Vice President, Regulatory Affairs

Electronic Submission Specifications

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Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	12.1.5337.5000
Virus Definition Date	**06**/11/2017 Rev.1
Submission Size	Approx. 3.1 MB

The IT point of contact for this submission is:

Name	Elena Renaud
Phone Number	(480) 500-3166
Email Address	erenaud@insysrx.com

August 21, 2017

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

REMS Final for approved NDA 202788, Supplement S-018

RE: NDA 202788: SUBSYS® (Fentanyl Sublingual Spray) for the management of breakthrough cancer pain
Sequence No. 0130: PRIOR APPROVAL SUPPLEMENT - REMS Final for approved NDA 202788, Supplement S-018

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011, for Insys Development Company, Inc.'s SUBSYS® (Fentanyl Sublingual Spray), which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013. Reference is also made to the REMS Modification Notification letter received on April 10, 2017. Reference is also made to the Information Request E-mail communication received on July 12, 2017, from Safety Regulatory Project Manager Wendy Brown to incorporated agency's comments on the REMS Materials.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Insys hereby notifies FDA of submission of the REMS modification, including the final formatted REMS document, materials including website screenshots, and REMS Supporting Document as separate files, as well as a compiled document for posting on the FDA REMS website requested by the FDA in the Information request, to the DMF #027320 in eCTD sequence 0031 on August 18, 2017.

If you have any questions regarding this submission, please contact me by telephone at (480) 500-3150 or by email at ssherman@insysrx.com.

Sincerely,

Stephen Sherman
Sr. Vice President, Regulatory Affairs

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

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Anti-Virus Program	Symantec Endpoint Protection Edition
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Submission Size	Approx. 2.69 MB

The IT point of contact for this submission is:

Name	Elena Renaud
Phone Number	(480) 500-3166
Email Address	erenaud@insysrx.com

Won, Katherine

From: Won, Katherine
Sent: Tuesday, August 21, 2012 2:57 PM
To: lauren.wind@weinberggroup.com
Cc: Sullivan, Matthew; Liberatore, Mark
Subject: REMS assessment for NDA 202788 Subsys (fentanyl) sublingual spray

Hello Ms. Wind,

We are reviewing your REMS assessment dated June 25, 2012, for NDA 202788 Subsys. We are initiating a 90-day discussion period with all the sponsors of TIRF products, including Insys Therapeutics, regarding the first TIRF REMS assessment. We will contact you soon to further discuss this issue.

Sincerely,
Katherine

Katherine S. Won PharmD, MBA
LCDR, U.S. Public Health Service
Safety Regulatory Project Manager
Division of Anesthesia, Analgesia and Addiction Products
FDA/CDER/OND/ODEII
10903 New Hampshire Ave.
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Silver Spring, MD 20993
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Email: Katherine.Won@fda.hhs.gov

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/s/

KATHERINE S WON
08/21/2012

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

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Application #(s):	NDA 202788, MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment REMS ASSESSMENT PLAN REVISION
Communication ID:	(COR-SEC901REMS-10) (COR-SEC901REMS-17)
Drafted by:	M.Liberatore 7/25/14, 8/6/14, 8/12/14, 8/15/14, 8/20/14
Clearance History:	JRacoosin 7/27/14 K. Lehrfeld 8/6/14 P. Jani/8-12-14, 8-15-14 SRT 8/14/14
Finalized:	M. Liberatore 8/21/14
Filename:	
Use Statement:	
Notes:	

Version: DARRTS 06/03/2012

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT
REMS ASSESSMENT PLAN REVISION

Insys Therapeutics, Inc.
444 South Ellis Street
Chandler, AZ 85224

Attention: Willene M. Brondum
Senior Manager, Regulatory Affairs

Dear Ms. Brondum:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subsys (fentanyl) sublingual spray, 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg.

We also refer to your December 30, 2013, submission containing the 24-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. In your one-year assessment report, information regarding the number of enrolled pharmacies from government agencies as well as other integrated systems/mail order data was presented. These categories are absent from your 24-month assessment report. In light of the REMS compliance issues experienced by at least two federal closed systems (the VA and DOD), in future assessment reports, report on the number of enrolled pharmacies in federal and other integrated systems.

2. Although the percentage of Patient-Provider Agreement Forms (PPAFs) received in the 10-day window between patient enrollment and receipt by the REMS program improved from the 12-month report figure (46% vs. 37%), continue to employ strategies that will improve the percentage of PPAFs received in the 10-day window.

3. A total of 73 outpatient pharmacies are described as having an "*incomplete configuration*," though no reasons are provided as to why these 73 pharmacies remain in

this status. In all subsequent assessment reports, provide complete information regarding why certain pharmacies are not able to configure their systems.

4. In future assessment reports, provide the most recent American Association of Poison Control Centers (AAPCC) case narratives.

5. Regarding RADARS data submissions in the future provide:
    a. information about the protocols used to generate these data
    b. data from the RADARS Drug Diversion Program
    c. the numbers of patients identified to have taken TIRFs for all of the programs for which you present data.

6. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

7. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

8. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

9. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

Our January 4, 2012 approval letter described the REMS assessment plan. During the review of the first and second year TIRF REMS assessment reports, changes to some of the metrics in the assessment plan were discussed both internally as well as with the TIRF REMS Industry Group (TRIG). The revisions provided in this letter serve to further tailor the metrics to those that are most informative regarding the operation and effectiveness of the TIRF REMS program. In brief, the revised REMS assessment plan comprises:

- Scaled back reporting of TIRF utilization data that focuses on the stakeholders enrolled, inactivated, and the numbers of stakeholders affected by enrollment delays
- Refocused dispensing activity data that includes stratification by closed/non-closed systems.

- A plan to assess non-compliance with the REMS that includes annual audits of randomly selected closed systems and inpatient systems.
- Safety surveillance that will consist of one comprehensive report that includes spontaneous adverse event data from all of the drugs under the TIRF REMS and that will focus on four categories of adverse events: addiction, overdose, death, and pediatric exposures.
- Continued use of stakeholder knowledge surveys to help inform whether the goals of the REMS are being met.

The complete revised REMS assessment plan is attached (see Appendix).

If you have any questions, call Vaishali Jarral, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Revised Assessment Plan

APPENDIX: REVISED ASSESSMENT PLAN

Assessment Plan for TIRF REMS

1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively)
    a. Patient Enrollment:
        i. Number of unique patients enrolled
        ii. Number of patients inactivated
    b. Prescriber Enrollment:
        i. Number of prescribers enrolled
        ii. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
        iii. Number of prescribers inactivated
    c. Pharmacy Enrollment:
        i. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities);
        ii. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
        iii. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);
    d. Distributor enrollment:
        i. Number of distributors enrolled
        ii. Number of distributors inactivated

2. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)
    a. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity

b. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)

c. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons

d. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized

e. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF

f. Number of prescriptions dispensed after ten days without a PPAF in place

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described

b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

c. Call center report with

i. Overall number of contacts

ii. Summary of frequently asked questions

iii. Summary of REMS-related problems reported

d. Description of corrective actions taken to address program/system problems

4. TIRF REMS Access Non-Compliance Plan: The TIRF sponsors should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Numbers of prescription authorizations per closed system

iii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program. Data to include the 12 month

period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).

iv. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

b. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period
These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program

iii. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

c. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:

i. Description of how the NCRT defines a non-compliance event

ii. Description of how non-compliance information is collected and tracked

iii. Criteria and processes the Team uses to make decisions

iv. Summary of decisions the Team has made during the reporting period

v. How the Team determines when the compliance plan should be modified

d. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action

e. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences

f. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified

h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

i. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

5. Safety Surveillance (data collected per reporting period):
    a. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures
    b. TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:
        i. Line listings under each category of adverse events of interest as listed above
        ii. Line listings should provide at a minimum the following information (see sample table provided):
            1. Identifying case number
            2. Age and Gender of the patient
            3. Date of the event as well as of the report
            4. The Preferred Terms
            5. Indication of TIRF use
            6. Duration of TIRF therapy
            7. Concomitant medications
            8. Event Outcome
        iii. Other metrics of interest include:
            1. Number of event reports in each event category of interest
            2. Counts of adverse events related to inappropriate conversions between TIRF products
            3. Counts of adverse events related to accidental and unintentional exposures
            4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients
        iv. Duplicate cases are identified and eliminated

v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events

vii. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs
ii. Surveys conducted at substance abuse treatment programs
iii. College surveys
iv. Poison control center data
v. Impaired health care workers
vii. Drug-related hospital emergency department visits
viii. Drug-related deaths
ix. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

6. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages

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/s/

JUDITH A RACOOSIN
08/21/2014

DOCUMENT INFORMATION PAGE

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Application #(s):	NDA 202788 MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment
Communication ID:	(COR-SEC901REMS-10)
Drafted by:	M. Liberatore 5/27/15
Clearance History:	DRISK 7/7/15, 7/16/15 J. Racoosin 7/16/15 K. Compton Jani for M. Sullivan/7-28-15 SRT 7/22/15
Finalized:	M. Liberatore 8/3/15
Filename:	
Signatory Authority:	DDS, Division Director, or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	
Notes:	

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END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT

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

Attention: Stephen Sherman
Vice President, Regulatory Affairs

Dear Mr. Sherman:

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

We also refer to your December 29, 2014, submission containing the 36-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. We are not able to assess whether the REMS is meeting its goals. The absence of spontaneous adverse event reports citing either use of a TIRF in opioid non-tolerant individuals or inappropriate conversions between TIRF products is not informative because spontaneous reporting systems are subject to under-reporting of adverse events. In addition, the accidental pediatric exposure data presented in the Assessment Report are difficult to assess due to unequal assessment periods and small numbers of cases. Lastly, the survey results indicate areas of low awareness of some important safe use messages.

2. In order to assess the TIRF REMS goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients, conduct the following analysis: Identify a health care database that includes an adequate number of TIRF product users. Within that database, by year, provide the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting. Determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. Provide these data separately for

patients receiving an opioid analgesic within the 7-days prior and within the 30-days prior to the initial TIRF prescription.

Before embarking on this analysis, provide to FDA your choice of database and the estimated number of TIRF users in the database so that we can determine if the number is adequate.

3. We are not able to establish whether the TIRF REMS is achieving the goal of preventing inappropriate conversion between TIRF medicines. In order to better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely. Conduct a persistency analysis based on the data available on the prescriptions processed through the switch system used by retail pharmacies. This analysis should demonstrate the number of patients starting on a TIRF and follow them over weeks and months to summarize their treatment course and change in therapy. The TIRF products can be grouped together, and the specific drug does not need to be disclosed. Following the discontinuation of the TIRF, the persistency analysis should also depict what treatment option the patient uses next. This will be either full discontinuation or switching to another TIRF product. There may be gaps in between prescriptions; propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF and provide a rationale for selection of that gap length.

4. Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues.

5. There has been a notable increase in mean and median prescription processing times during this reporting period versus the previous period. Investigate and identify the causes of these increasing delays in prescription processing and report the results in your next Assessment Report.

6. None of your reported spontaneous adverse events include a root cause analysis as specified in the Assessment Plan. In your subsequent Assessment Reports, include a root cause analysis of adverse events reported to the TRIG Sponsors.

7. The closed system pharmacies continue to struggle with the REMS authorization processes. Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report.

8. Your presentation of the non-compliance data in the submitted report is disorganized. Various events are described in Assessment Report Section 6.1.1 and in the Report's Tables 21 and 22. Events found in one of these areas often sound similar to events reported in other areas, and thus it is unclear whether these different sources are referring to distinct events or are describing the same event. In addition, while your Report's Table 21 indicates seven

instances where closed system pharmacies dispensed drugs without obtaining authorization, the audit conducted by the TRIG reports 513 such incidents. Organize and harmonize these various components into one clear presentation that is comprehensive and eliminates duplication.

9. Provide the criteria as to how compliance decisions are made by the NCRT and include your non-compliance protocol with your next Assessment Report.

10. In subsequent Assessment Report submissions of RADARS data, provide the following:

    a. A more detailed data analysis section that presents the statistical methods used, how calculations were performed, and the assumptions made, at the level of detail as provided in your April 2, 2015, response to the March 19, 2015, FDA Information Request. In addition, include a pre-post REMS means analyses and trend analyses (e.g. segmented regression analyses), statistically comparing event rates for a time-period immediately prior to full implementation of the TIRF REMS with an equivalent period of time after REMS implementation.

    b. Present the data at the dosage unit level as well as population and URDD levels.

    c. The RADARS treatment center data (Opioid Treatment Program and Survey of Key Informants Patients) programs are confounded by the fact that the number of treatment centers participating in each quarter fluctuates (although the overall numbers are generally increasing). In subsequent submissions, limit the presentation of treatment center data to centers that have contributed data in all of the time-periods assessed. In addition, provide the various versions of the survey instruments/pill cards in use throughout the time-periods assessed with dates provided indicating when each instrument was in use.

11. We remind you that the following comments related to the stakeholder surveys were provided in the August 21, 2014, letter to the TRIG. These revisions should be implemented in subsequent surveys along with the new survey revisions described in item 12 below.

    a. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

    b. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

    c. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the

CYP3A4 interactions with TIRFs. Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

d. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

12. Additional comments and recommended revisions to the stakeholder surveys that should be implemented in subsequent surveys follow below:

a. Patient survey
   i. In subsequent Assessment Reports, provide an analysis of how the demographics of the patient survey respondents compare to the demographics of actual TIRF patients.
   ii. For Question 4, remove Onsolis as a response option because it is no longer available.
   iii. Move Question 13b: *It is okay for patients to take TIRF medicines for headache pain* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.
   iv. Add Question 10a-e: *For which of the following conditions should you use a TIRF medicine?* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.

b. Pharmacist survey
   i. For Question 26, remove Onsolis as a response option because it is no longer available.
   ii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.
   iii. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.
   iv. Move Question 13c: *TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product* to Key Risk Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

c. Prescriber survey

i. In subsequent Assessment Reports, provide an analysis of how the demographics of the prescriber survey respondents compare to the demographics of actual TIRF prescribers.

ii. For Question 30, remove Onsolis as a response option because it is no longer available.

iii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.*

iv. Move Question 7b: *Death has occurred* in opioid non-tolerant patients treated with some fentanyl products to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients.*

v. Move Question 10d: *Dosing of TIRF medicines is not equivalent on a microgram to microgram basis* to Key Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

vi. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.

vii. Move Question 18b*: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

viii. Move Question 18c: *Instruct patients that if they stop taking their around the clock opioid medicine, they can continue to take their TIRF medicine* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

ix. Remove Question 19: *Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*

If you have any questions, call Wendy Brown, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-9140.

Sincerely,

{See appended electronic signature page}

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

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/s/

JUDITH A RACOOSIN
08/03/2015

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Application #(s):	NDA 202788 MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment
Communication ID:	(COR-SEC901REMS-10)
Drafted by:	M. Liberatore 9/29/16
Clearance History:	J. Racoosin 10/27/16, 11/8/16 D. Auth 11/1/16 Sullivan 11-9
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT

Insys Development Co.
c/o Insys Therapeutics, Inc.
1333 South Spectrum Blvd., Suite 100
Chandler, AZ 85286

Attention: Stephen Sherman
Sr. Vice President, Regulatory Affairs

Dear Mr. Sherman:

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

We also refer to your December 29, 2015, submission containing your assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) Products risk evaluation and mitigation strategy (REMS).

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. After review of the 48 month (5th overall) REMS assessment report for the Transmucosal Immediate-Release Fentanyl (TIRF) Products REMS, we conclude that it is not possible to determine whether the overarching goal of the REMS - to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors is being met.
   a. The first objective (prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients) is not being achieved. In the TIRF REMS Industry Group's (TRIG's) assessment of opioid tolerance, approximately 42% of patients prescribed TIRF products were not opioid tolerant. It is important that the TRIG further investigate this issue.

   b. It is not possible to determine if the second objective (preventing inappropriate conversion between TIRF medicines) is being met. Though no instances of inappropriate conversions were submitted as a spontaneous report, the persistency analysis provided indicates that the number of patients who may be exposed to inappropriate conversion between TIRF medicines may be as high as 17.1-20.5% of patients receiving TIRF medicines. Further assessment of these findings is also warranted.

c. It is also not possible to determine if the third objective (preventing accidental exposure to children and others for whom it was not prescribed) is being met. The case reports for this metric remain quite low thus challenging the ability to assess the impact of the REMS on this objective, particularly since the case reports do not provide enough information to conduct a root cause analysis (RCA).

d. The fourth objective (educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines) is partially being met. Overall, patients, prescribers, and pharmacists seem to have an adequate understanding of most of the key risk messages related to preventing inappropriate conversion, accidental exposure, and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however, all groups had a lower awareness of the need to only prescribe and dispense TIRF medicines to appropriate patients.

2. In order to address the deficiencies outlined in 1a, b, c, and d, we have the following comments:

a. Regarding the assessment of opioid tolerance submitted in the 48 month assessment, approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG needs to further investigate this concerning finding. A timeline for a plan to further evaluate this finding should be submitted with the February 17, 2017, submission of the 60 month REMS assessment survey results. At a minimum, further evaluation of this finding will include product-specific assessment of opioid tolerance that each member sponsor will submit only to their NDA or ANDA. Additional details regarding this evaluation will be communicated in a separate letter.

b. Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to "inappropriate conversion between TIRF medicines" is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the February 17, 2017, submission of the 60 month REMS assessment survey results; if additional time for protocol development is needed, please request an extension.

c. We would like to schedule a meeting to discuss opportunities for obtaining additional data on accidental exposure to children and others for whom TIRF products are not prescribed, as well as to discuss possible ways to address the low

awareness of the need to prescribe and dispense TIRF medicines to appropriate patients.

3. Additional comments on the 48 month assessment:

a. In the FDA's 36-month REMS Assessment Acknowledgement Letter (date August 3, 2015), the TRIG was asked to "Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues."

In the 48 month assessment report, the TRIG responded that: "Based on…analysis, there is no barrier to patient access and further outreach is unwarranted." The TRIG states that 516 prescribers (8.6%) chose to not re-enroll and that these prescribers had an average of no more than four prescriptions total over the course of the reporting period. However, the reasons why these prescribers withdrew from the program are unknown as are the reasons why 1,134 prescribers had their enrollment expire this reporting period and remain expired. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented.

It is therefore important that the TRIG proceed with conducting an "…outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons… (w)e are concerned about potential patient access issues." Submit a timeline for the plan to conduct this outreach in the February 17, 2017, submission of the 60 month REMS assessment survey results.

b. There continues to be a steady increase in mean and median prescription processing times during this reporting period versus the previous periods. The TRIG was previously asked to investigate this finding, but did not do so, instead stating that this finding may be due to a lower number of prescriptions with at least one initial REMS-related rejection this reporting (1,735) period as compared to the 36-month report (3,738). These differences cited by the TRIG do not appear to be so large as to account for some sort of number skewing induced by a small sample size. The TRIG needs to investigate and identify the causes of these increasing delays in prescription processing as these are potential indicators of access barriers.

c. The TRIG Protocol for Corrective Actions for Instances of Non-Compliance contains few concrete criteria or decision trees as to how to deal with episodes of non-compliance. Thus it is unclear to us what types of non-compliance actions would reliably lead to suspension or deactivation. The TRIG should add

increased specificity to the Non-Compliance Review Team (NCRT) protocol as well as to the Supporting Document of the REMS.

In addition, it is concerning that the TRIG's criteria for an incident of an individual prescriber non-compliance with Patient-Prescriber Agreement Form (PPAF) requirements needs to involve at least "5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date." These criteria would appear to potentially lead to an under-reporting of PPAF non-compliance. The TRIG should explore mechanisms to capture lower levels of non-compliance.

d. Regarding the three instances where a non-closed system pharmacy dispensed a TIRF product after a TIRF REMS rejection, all three reports were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The TRIG should develop a more active mechanism by which to identify and prevent such occurrences.

e. Although results for both governmental (Veteran's Health Administration and Department of Defense) and closed-pharmacy systems appear to have improved from the 36-month audit, they continue to be unsatisfactory. The 36-month REMS Assessment Acknowledgement Letter requested that the TRIG "Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report." The TRIG has issued the following response: "The TRIG has determined that the current prescription authorization volume for closed-system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time." An absence of complaints does not necessarily mean that a closed pharmacy system process is functioning optimally. These audits are likely one of the best sources of information regarding the performance of these closed-system pharmacies in meeting the REMS requirements. If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance. In addition, the TRIG should be sure to include both governmental entities in the 60-month audit so that their performance in the REMS can continue to be monitored.

Lastly, the TRIG presents the process times for prescriptions that have experienced at least one REMS-related rejection. However, data on the overall processing time of a prescription that does not meet with any rejections is unclear. Given that one of the pieces of information solicited during the closed-system audits is "Date and time of each prescription transaction," this is an excellent opportunity for the TRIG to assess prescription processing times for prescriptions that do not experience any REMS-related rejections. The TRIG should add this component to their closed-system audits.

f. For the Inpatient Pharmacy audits, six inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current inpatient pharmacy enrollment form, the pharmacy only agrees to have their training audited. We are considering revisions to this enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment.

g. The TRIG reports a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs.

h. For subsequent submissions of Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) data that contain CII opioid comparators, expand the CII immediate-release opioid category to include oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen.

i. The Agency has increasing concerns about the use of RADARS data to assess some of the outcomes outlined in the TIRF REMS. Given the limitations of RADARS, the Agency believes that additional data sources that can track adverse outcomes of interest associated with the TIRF products are necessary, and the TRIG must study intermediate objectives more closely related to the REMS intervention. The FDA proposes a meeting with the TRIG to discuss and explore new approaches to assessing this REMS with the goal of gathering useful information to better understand the impact of the REMS and to improve the program going forward.

4. We refer to the July 21, 2016, FDA electronic communication in which comments on the patient, prescriber, and pharmacist surveys were conveyed based upon the 48 month REMS assessment results. We acknowledge the subsequent agreement between the Agency and the TRIG that the survey results for the 60 month TIRF REMS assessment will be submitted to the Agency on February 17, 2017.

If you have any questions, call Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director of Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JUDITH A RACOOSIN
11/10/2016

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 202788
Communication Type:	Correspondence
Communication Group:	Safety
Communication Name:	REMS Modification Notification
Communication ID:	COR-SEC901REMS-06
Drafted by:	M. Liberatore 2/6/17, 4/6/17
Clearance History:	DRISK 3/6/17 J. Racoosin 3/6/17 M. Sullivan4/7
Finalized:	M. Liberatore 4/10/17
Filename:	
Signatory Authority:	DDS, Division Director, or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e, the signature block on the letter will not change).
Use Statement:	FDA determines that a modification to an approved REMS is required
Notes:	Please ensure all review disciplines, including DRISK, have provided input on the letter

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END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202788

REMS MODIFICATION NOTIFICATION

Insys Development Co., Inc.
c/o Insys Therapeutics, Inc.
1333 South Spectrum Blvd. Suite # 100
Chandler, AZ 85286

Attention: Stephen Sherman
Vice President, Regulatory Affairs

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBSYS (fentanyl sublingual spray), which is part of a shared system Risk Evaluation and Mitigation Strategy (REMS), the Transmucosal Immediate-Release Fentanyl (TIRF) REMS access program.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENT

The TIRF REMS, of which SUBSYS is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on December 24, 2014. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We also refer to our letters dated March 22, and August 31, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for SUBSYS, and the approval of the safety labeling changes on December 16, 2016. Those labeling changes pertained to the risks of misuse, abuse, addiction, overdose, death and neonatal opioid withdrawal syndrome; serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; androgen deficiency; and profound sedation, respiratory depression, coma, and death associated with the concomitant use of opioid analgesics and benzodiazepines or other central nervous system depressants, including alcohol.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that the approved TIRF REMS, of which SUBSYS is a member, must be modified to ensure that the benefits of the drug outweigh its risks. This determination is based on the need to make changes to the the approved REMS consistent with the safety labeling changes approved on December 16, 2016.

Your proposed modified REMS must include modifications to the REMS document, appended materials, and REMS supporting document consistent with the safety label changes approved on December 16, 2016.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on June 5, 2012.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications in track changes.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes in track changes.

Because we have determined that a modified REMS as described above is necessary to ensure the benefits of SUBSYS outweigh the risks, you must submit a proposed REMS modification within 60 days of the date of this letter.

The TIRF REMS Implementation Group (TRIG) should submit the proposed modified REMS to DMF 27320. In accordance with 21 CFR §§ 314.97 and 314.70, and as described in FDA's draft guidance for industry on *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (April 2015), REMS modifications due to approved safety labeling changes are considered major changes that require approval prior to distribution; therefore, submit your cross-reference submission as a Prior Approval Supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 202788/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 202788/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

If you do not submit electronically, please send 5 copies of your submission.

If you have any questions, call Mark Liberatore, PharmD, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JUDITH A RACOOSIN
04/10/2017