

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205525Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205525

SUPPL # 000

HFD # 180

Trade Name **Syndros**

Generic Name **dronabinol oral solution**

Applicant Name **Insys Development Company, Inc.**

Approval Date, If Known **July 1, 2016**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)2

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

YES ☒ NO ☐

Response:

The sponsor claims that the "clinical data" from the Human Abuse Potential Study are essential to the approval of the application.

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

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

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three Year

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 018651 Marinol (dronabinol capsules)

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets

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

YES ☒ NO ☐

Response:

The sponsor cites the following clinical investigation INS-13-017: A single-dose, double-blind, double-dummy, randomized, placebo-and active-controlled crossover study to evaluate the abuse potential of dronabinol oral solution in recreational cannabinoid users.

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

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

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

YES ☒ NO ☐

Response:

The sponsor cites 21 CFR 314.10(d)(3) and the advice given by CSS on 12/17/2013 that without this clinical data, the application would be subject to refuse to file.

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

The following clinical investigation in the application that is essential to the approval is INS-13-017: A single-dose, double-blind, double-dummy, randomized, placebo-and active-controlled crossover study to evaluate the abuse potential of dronabinol oral solution in recreational cannabinoid users.

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

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

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

Investigation #1 **INS-13-017**

YES ☐ NO ☒

Investigation #2

YES ☐ NO ☐

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

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

Investigation #1 **INS-13-017**

YES ☐ NO ☒

Investigation #2

YES ☐ NO ☐

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

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

The following clinical investigation in the application is “new” and is essential to the approval is INS-13-017: A single-dose, double-blind, double-dummy, randomized, placebo-and active-controlled crossover study to evaluate the abuse potential of dronabinol oral solution in recreational cannabinoid users.”

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

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

Investigation #1

!
!

IND # 75228

YES ☒

! NO ☐
! Explain:

Investigation #2

YES ☐

!
!
! NO ☐
! Explain:

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

Investigation #1

YES ☐
Explain:

!
!
! NO ☐
! Explain:

Investigation #2

YES ☐
Explain:

!
!
! NO ☐
! Explain:

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

YES ☐ NO ☒

If yes, explain:

=====

Name of person completing form:
Maureen Dewey, MPH
Senior Regulatory Project Manager, DGIEP
Date: 4/4/2016

Wen-Yi Gao, M.D.
Medical Officer and Clinical Reviewer, DGIEP
Date: 4/4/2016

Andrew Mulberg, M.D.
Title: Deputy Director, DGIEP
Date:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MAUREEN D DEWEY
07/01/2016

ANDREW E MULBERG
07/01/2016

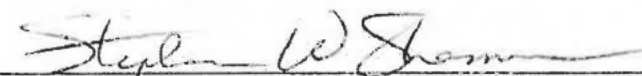
Debarment Certification

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

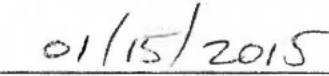
This is to certify:

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

List of convictions: None



Stephen Sherman
Vice President, Regulatory Affairs
Insys Therapeutics, Inc.



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205525 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Syndros Established/Proper Name: dronabinol Dosage Form: oral solution		Applicant: Insys Development Company, Inc. Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: DGIEP
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:
<i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>		
❖ Actions		
- Proposed action - User Fee Goal Date is 7/1/2016		☒ AP ☐ TA ☐ CR
Previous actions (<i>specify type and date for each action taken</i>)		☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Reactive Statement
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action and date AP 7/1/16
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included 7/01/2016
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	☒ Included 6/23/2016; 6/13/2016; 3/11/2016; 9/28/2015; 6/1/2015
❖ Proprietary Name	10/13/2015; 10/9/2015
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: ☐ 8/6/2015 DMEPA: ☐ 3/24/2016 Matt Barlow DMPP: 6/13/2016 Karen Dowdy OPDP: ☐ Meeta Patel 2/11/2016 SEALD: ☒ None CSS: ☒ None 2/26/2016 Product Quality ☐ None Other: Labeling
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	8/6/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) 3/15/2016
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>2/3/2016</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i>	Refuse to File Letter 10/10/14
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	4/26/2016; 3/17/2016
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☐ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☐ No mtg 4/17/2012
EOP2 meeting <i>(indicate date of mtg)</i>	☐ No mtg 5/13/2010
Mid-cycle Communication <i>(indicate date of mtg)</i>	☐ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☐ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☐ None
Division Director Summary Review <i>(indicate date for each review)</i>	☐ None 7/1/2016
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None 5/20/2016
PMR/PMC Development Templates <i>(indicate total number)</i>	☐ None 5

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☐ No separate review 5/20/2016
• Clinical review(s) (indicate date for each review)	4/1/2016
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Page 48 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☐ None QTIRT (10/27/15) DEPI (11/25/2015) DPV (1/12/2016) OSE (3/15/2016) DNP (3/21/2016) DMEPA (3/24/2016) DPMH (6/30/2016; 4/11/2016; 4/1/16; 12/3/15) DPP (4/27/2016)
❖ Controlled Substance Staff reviews and Scheduling Recommendation (indicate date of each review)	☐ N/A 6/29/2016; 4/22/2016; 2/26/2016
❖ Risk Management • REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) • REMS Memo(s) and letter(s) (indicate date(s)) • Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Statistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☐ None DBIV 1/4/2016

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 3/1/2016
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None requested Memo 8/4/2015
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☐ No separate review
• Supervisory Review <i>(indicate date for each review)</i>	☐ No separate review 6/28/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None 2/22/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☐ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☐ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	☐ None 7/01/2016; 2/29/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	☐ None CDRH 6/7/2016; 3/24/2016 (2); 3/22/2016; 3/10/2016 (2); 3/9/2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2/24/2016
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change))</i>	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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MAUREEN D DEWEY
07/01/2016

From: [Dewey, Maureen](#)
To: [Stephen Sherman](#)
Cc: [Dewey, Maureen](#)
Subject: NDA 205525 dronabinol Labels
Date: Wednesday, June 29, 2016 9:34:34 AM
Attachments: [FDA final clean PI.docx](#)
[FDA Final tracked PI.pdf](#)
[FDA final clean IFU.docx](#)
[FDA final clean Patient Packet Info.docx](#)
[FDA final Patient Packet Info.pdf](#)
[FDA final IFU.pdf](#)

Mr. Sherman:

Reference is made to your June 1, 2015 resubmission to your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for dronabinol oral solution.

On June 23, 2016, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (PI, PPI and IFU). We request that you resubmit labeling that addresses these issues by June 30, 2016.

Please confirm receipt of this correspondence.
Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager | DGIEP | ODE III | OND | CDER | FDA | 301.796.0845 | FAX 301.796.9904
maureen.dewey@fda.hhs.gov

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32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MAUREEN D DEWEY
06/29/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 26, 2016; 10:00 AM – 11:00 AM
Application Number: NDA 205525
Product Name: dronabinol oral solution
Sponsor/Applicant Name: Insys Development Company, Inc.
Call Information: (b) (4)
Subject: Dronabinol Scheduling Recommendation

FDA Participants:

OFFICE OF THE CENTER DIRECTOR (OCD)

Douglas C. Throckmorton, M.D., Deputy Director Regulatory Programs

Controlled Substance Staff (CSS)

Michael Klein, Ph.D., Director

Silvia Calderon, Ph.D., Pharmacologist

Martin Rusinowitz, M.D., Medical Officer

Dominic Chiapperino, Ph.D., Regulatory and Liaison Team Leader

Corinne Moody, Science Policy Analyst

OFFICE OF EXECUTIVE PROGRAMS (OEP)

Virginia L. Behr, Ombudsman

ODE III

Julie Beitz, M.D., Director

Amy Egan, M.D., Deputy Director

Maria Walsh, R.N., M.S., ADRA

Richard Ishihara, Regulatory Scientist

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Andrew Mulberg, M.D., Deputy Director, DGIEP

Joette Meyer, Pharm.D., Associate Director for Labeling

Stephanie Omokaro, M.D., Medical Team Leader

Kevin Bugin, Acting Chief, Project Management Staff

Maureen Dewey, Regulatory Project Manager, DGIEP

Sponsor/Applicant Participants:

Insys Development Company, Inc.

John Kapoor, President & Chief Executive Officer

Ramesh Acharya, Executive Vice President, Scientific Operations

Santosh Vetticaden, Senior Vice President and Chief Medical Officer

Dan Brennan, Executive Vice President and Chief Operating Officer

Stephen Sherman, Senior Vice President, Regulatory Affairs

Elena Renaud, Senior Manager, Regulatory Affairs

Dinesh Anugu, Regulatory Affairs Associate

1.0 BACKGROUND:

NDA 205525 is a 505(b)(2) application for dronabinol oral solution (4.25 mg/0.85 ml). The product is co-packaged with a dosing syringe. Dronabinol oral solution is a new formulation of dronabinol, and contains synthetic delta-9-tetrahydrocannabinol (delta-9-THC).

The applicant is relying for approval on the FDA's finding of safety and effectiveness for Marinol (dronabinol capsules) approved on May 31, 1985. The applicant proposes the same indications as Marinol, which are as follows:

- 1) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and
- 2) anorexia associated with weight loss in patients with AIDS.

During a teleconference held on March 2, 2016, CSS informed the applicant of the Schedule II recommendation for dronabinol oral solution. The applicant contacted the CDER Ombudsman to notify the Agency that they disagreed with the CSS scheduling recommendation. On March 10, 2016, the applicant submitted a response containing clinical and nonclinical data to support their request for a Schedule III recommendation. The amendment was received on March 10, 2016 and extended the PDUFA goal clock to July 1, 2016.

On April 25, 2016, the Agency provided the applicant with responses to the March 10, 2016, amendment and conclusions that the Schedule II recommendation remains unchanged. The purpose of this telecon was to discuss the criteria used for a scheduling determination.

2.0 DISCUSSION:

CSS Criteria for Schedule II recommendation:

1. The Product (i.e., dronabinol oral solution) is easily manipulated for abuse by inhalation and oral routes.
2. The formulation of the Product has important differences from Marinol that facilitate product manipulation. Product has inherent PK/PD properties that make it potentially more abuseable than Marinol.
3. Physical manipulation of the Product is easier than that of Marinol.
4. The Product can easily be abused by inhalation (smoking and vaping).
5. As a sweet alcoholic solution of dronabinol, the Product is formulated to be appealing to users and abusers.
6. The Product mediates a greater array of psychiatric AEs.
7. The risk of overdose with dronabinol products is described in the Marinol and Dronabinol Oral solution labels.
8. The human abuse potential (Clinical Trial INS-13-017) study confirmed that the Product has an abuse potential comparable to that of Marinol in recreational cannabis users *when taken as prescribed, following administration of single doses no greater than 30 mg.*

9. The abuse potential of dronabinol oral solution relative to that of Marinol when administered via the sublingual route was not addressed in human abuse potential studies.

Discussion:

The applicant acknowledged the CSS recommendation and rationale but noted that they continue to respectfully disagree with the recommendation. They inquired about whether upon an initial agreement to a Schedule II, the Agency would consider rescheduling if the sponsor implemented a postmarketing monitoring program and submitted quarterly Periodic Adverse Drug Event Reports (PADER) for review. The Agency acknowledged that there is a precedent for rescheduling drugs post-approval and that the formal process includes a petition to the DEA and HHS.

Alternatively, the applicant asked if the Agency would consider approving dronabinol oral solution as a Schedule III with a post-marketing requirement to conduct an abusability study. The Agency cautioned that this approach was not recommended and post-marketing studies are often imprecise, subjective and lack of an abuse signal is difficult to interpret.

The Agency focused additional discussion on the importance of comparing dronabinol oral solution to the Marinol, and not to marijuana. Recovery of liquid volume from Marinol capsules and the endpoint of Liking from the abuse potential study, which compared dronabinol oral solution to Marinol were also discussed.

The Agency requested the sponsor submit for review a response containing a direct comparison between Marinol and dronabinol oral solution using the following criteria:

- Taste
- Ethanol content
- Ease of manipulation
- Risk of diversion
- Attraction to diversion
- Nature of high (including difference in high)
- Concentration of THC
- Route of administration

3.0 ACTION ITEMS:

The applicant agreed to submit their response formally to the NDA. The Division agreed to review the submission and provide a timely response. The Ombudsman reminded the applicant that any formal submission will be reviewed by the Division; however, the Ombudsman remains a resource to the applicant.

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/s/

MAUREEN D DEWEY
04/28/2016

From: Dewey, Maureen
To: ["Stephen Sherman"](#)
Subject: NDA 205525 Telecon Discussion Points
Date: Monday, April 25, 2016 4:10:00 PM
Attachments: [Telecon April 26.pdf](#)

Mr. Sherman:

Attached please find comments for your review. We are available for a discussion tomorrow, April 26th at 10:00am.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager | DGIEP | ODE III | OND | CDER | FDA | 301.796.0845 | FAX
301.796.9904
maureen.dewey@fda.hhs.gov

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Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dronabinol oral solution.

In advance of our teleconference scheduled for Tuesday, April 26, 2016 from 10:00 AM – 11:00 AM, please review the Agency's comments regarding your amendments dated March 10 and 18, 2016, regarding the scheduling of your proposed product and carton and container labeling.

Controlled Substance Staff

After consideration of the totality of the data (clinical and in vitro) submitted by the Sponsor, upon approval of the NDA, CSS recommends rescheduling of SYNDROS from Schedule I to Schedule II of the CSA.

1. *The formulation of the Product has important differences from Marinol that facilitate product manipulation. Data from submitted in vitro studies do not support your claim that the Product and Marinol capsules are chemically similar. The Product, in comparison to Marinol capsules, can be easily concentrated by evaporation when exposed to minimal heat. In addition, a higher percentage of dronabinol is extracted from the Product with methylene chloride than from Marinol capsules (using the best solvent for extraction that you identified). Methylene chloride extracted on average over 85 % of the API from the Product solution, while on average 65 % of API was extracted from the Marinol capsules in ethanol (an efficient extraction solvent used with Marinol). You concluded that extraction of the API from the Product and from dronabinol capsules is feasible. You further concluded that the extraction of the API from the Product is not more efficient or that it would not afford larger quantities of the API than the extraction from Marinol capsules, based on the assumption that a high volume of methylene chloride would have to be used to recover large quantities of dronabinol from the oral solution and that it will take longer to evaporate this solvent. However, the use of higher volumes of the solution and of extraction solvents does not impede the ability to extract larger amounts of dronabinol from the oral solution. In some instances, the use of larger volumes may actually increase the efficiency of the extraction by decreasing the losses that result from working with smaller extraction samples. Overall, in vitro manipulation studies demonstrate that the Product can be successfully manipulated to afford highly concentrated extracts in solvents that can be easily evaporated to give high content dronabinol residues that can be abused by smoking or through other routes of abuse.*

Insys' responses to each item in Question #1 are discussed below. CSS responses are in **bold font**.

1. a. Agency Comment: The formulation of the Product has important differences from Marinol that facilitate product manipulation.

Insys Response: As demonstrated in the accompanying video, Marinol capsules can be easily cut open to obtain the sesame oil solution that contains 3 to 12 times more dronabinol per mL than SYNDROS.

CSS Response:

The argument presented compares volumes as opposed to milligram amounts in products and extracts and is therefore not relevant. Abusers can drink directly, from the dispensed bottle, the 30 mL of the sucralose-sweetened 50 % w/w alcoholic solution containing 150 mg of dronabinol, which based on bioequivalence studies are equivalent to 176 mg of dronabinol in sesame oil.

In the video provided, you show that it took less than 1 minute to collect 1 mL of the sesame oil formulation by pinching and squeezing seven 10 mg Dronabinol capsules. You report that 93-97% of the content of the capsules is collected in this manner. However, your analysis does not consider the amount (mg) of sample lost in the manipulation of the sample. You report that the average amount of dronabinol contained in 1 mL of the sample is 54.85 mg. Considering that 54.85 mg of dronabinol are recovered from a sample that contains a total of 70 mg of dronabinol (7 capsules of Marinol 10 mg strength), 21% percent of the sample is lost in the initial manipulation process.

1.b. Agency Comment: The Product, in comparison to Marinol capsules, can be easily concentrated by evaporation when exposed to minimal heat:

Insys Response: Drying studies conducted and documented in CHP12009 submitted in S0000 (initial NDA submission) demonstrated that 2 mL of SYNDROS oral solution requires from 7 min (using microwave) to 1.5 hours (using heat lamp) to dry and results in residue ranging from 330 mg to 550 mg. This residue contains formulation excipients and is a viscous liquid, not a dry solid powder suitable for further manipulation for oral or inhalation abuse. The amount of dronabinol contained in this residue ranges from 9.3 mg to 9.7 mg. The resulting oily residue from SYNDROS is similar to the contents from a single capsule of Marinol, which does not require any manipulation. These data suggest that Marinol would be preferred choice for ease of abuse.

Moreover, Marinol capsule content can be easily manipulated compared to dronabinol oral solution in a fraction of the time it takes to dry SYNDROS oral solution. Moreover, because the capsule content is sesame oil, it can be used directly without any further manipulation into baking ingestible forms of dronabinol e.g., brownies. These data indicate that Marinol capsules are easier to manipulate than SYNDROS oral solution.

CSS Response:

You did not conduct smoking studies to conclude that Marinol would be the preferred choice of abusers.

Your point that the sesame oil formulation can be used in the manufacture of edibles is not relevant. Abusers will have easy access to a THC drink of pharmaceutical quality when taking SYNDROS.

1.c. Agency Comment: A higher percentage of dronabinol is extracted from the Product with methylene chloride than from Marinol capsules (using the best solvent for extraction that you identified).

Insys Response: As suggested by the Agency, Insys agrees that the use of a higher volume of extracting solvent can extract a larger quantity of dronabinol. Insys conducted additional extraction studies where equal volumes, 1 mL of SYNDROS oral solution and 1 mL content from Dronabinol capsules (10 mg capsule), were extracted using 10 mL of the extracting solvents methylene chloride and ethanol, respectively for the two products. The amount of dronabinol extracted from Dronabinol Oral Solution was 4.75 mg (95 % of theoretical) and from Dronabinol Capsules was 51.1 mg (93% of theoretical). Previous studies used lower volumes of extracting solvents (2 mL) compared to the 10 mL used in these experiments as suggested by the Agency. Also, the additional experiments utilized equal volumes of each product for extraction in a head-to-head comparison (see Report CH.0030 for further details).

Based on the results of this comparison, Dronabinol Capsules provide 10.5 times the amount of dronabinol for abuse after extraction compared to the same amount of volume from SYNDROS oral solution. Results demonstrate that dronabinol capsules can be successfully manipulated to afford highly concentrated extracts in solvents that can be easily evaporated to provide a higher content of dronabinol residues that can be abused by smoking or through other routes of abuse compared to SYNDROS. Thus, Dronabinol capsules have a higher abuse potential than SYNDROS, but both have much less than the ubiquitous marijuana so prevalent in society.

CSS Response:

FDA did not request you to conduct additional studies increasing the volume of extraction. Our comment regarding the use of larger extraction volumes was intended to address your statement provided under the Study Report- Study CH022 (Page 6 of 6, lines 10-15, “Results Summary” section of Study Report- Study CH022). It states, “Considering that 5 mg and 10 mg capsules strengths are available it is possible to extract a larger quantity of Dronabinol from the same volume of sesame oil for Dronabinol capsules. Whereas for the oral solution, only one strength is available (5 mg/mL) and in order to recover larger quantities, higher volumes of oral solution will need to be extracted which will take longer to evaporate the extract.” CSS’s comment reflected on the fact that the use of higher volumes of the solution and of solvent should not be considered an impediment for a determined abuser to extract the large amount of dronabinol contained in SYNDROS.

Under the new experimental conditions percent extraction of dronabinol increased from 85% to 95% when working with the oral solution and increased from 66 % percent to 73

% overall yield when using Marinol capsules. You reported a 93.5% extraction yield when working with the Marinol capsules, however this calculation does not take into consideration that when working with the Marinol capsules, on average, 21.5 percent of the sample was lost in the handling process of the sesame oil formulation.

Based on your most recent studies, it can be predicted that approximately the totality of the dronabinol contained in the 30 mL of the dispensed product could be easily extracted when using higher extraction solvent volumes.

2. The Product has inherent PK/PD properties that make it potentially more abuseable than Marinol. Although the Product and Marinol capsules can both be abused by oral ingestion, the Product may serve as an easily accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) for purposes of abuse. Additionally, and not addressed in your submission, the Product can be taken sublingually and absorbed bypassing oral ingestion. This raises the potential for another abuseable route of administration of high doses of dronabinol at levels that are not practically achievable with Marinol.

Insys Response:

Insys does not agree that SYNDROS oral solution has more abuse potential than Marinol due to the inherent PK/PD properties of the Product. The active moiety has not been structurally or chemically modified in any way that would result in different PK/PD characteristics. Further, it should be noted that Insys demonstrated bioequivalence between two products via an adequately conducted clinical trial (INS-12-015), confirming similar PK/PD characteristics for both products.

Marinol Capsules are available in 60-count bottles for the 10 mg strength [NDC0051- 0023-21], such that an intended abuser may obtain 4-times more (600 mg) of the total amount of active ingredient, dronabinol, than is contained in a bottle of SYNDROS (150 mg). This 4-fold lower concentration in SYNDROS confers a lower risk for abuse than Marinol. Further, it can be reasonably expected that even in the case of sublingual/buccal administration the higher concentration of dronabinol in Marinol will provide a greater absorption gradient leading to faster attainment of higher concentrations relative to SYNDROS. The latter is also likely to contribute to lower abuse potential for SYNDROS relative to Marinol.

Sativex, an oromucosal spray containing THC and CBD, is marketed in the United Kingdom and Canada by GW Pharmaceuticals. Each milliliter of Sativex contains 27 mg of dronabinol and 25 mg of CBD in 50% ethanol and (b)(4)% propylene glycol. It should be noted that even with smaller volumes of highly concentrated alcohol spray (approximately 5-fold higher concentration than SYNDROS) administered oromucosally, the T_{max} for THC is 1 hour (Sativex, Summary of Product Characteristics, May 20, 2015; GW Pharma). Further, holding large volumes of lower concentration liquid in the oral cavity for a prolonged period of time to facilitate sublingual absorption do not lend itself as a route for abuse. The maximum amount of volume that can be comfortably retained in the sublingual pocket is reported in the range of about 0.4 mL. Consequently, the sublingual/buccal route of administration presents a much lower potential for abuse for SYNDROS relative to Marinol.

Based on all of the above data, Insys submits that SYNDROS would have a lower potential for abuse relative to Marinol capsules.

CSS Response:

Clearly the API of both Marinol and SYNDROS are the same. The formulations are not. We maintain that an alcohol based sweetened dronabinol solution is more likely to be abused without the need for any manipulation when compared with that needed to abuse Marinol. While we agree that the active moiety in SYNDROS has not been structurally or chemically modified in any way compared to Marinol, we disagree that formulation differences would not result in different PK/PD characteristics. SYNDROS has a shorter T1/2 than Marinol. This might explain some of the PD differences.

We understand that the sublingual route of abuse of a liquid product may be difficult, but this has not been studied. It still remains more likely that SYNDROS has greater abuse potential sublingually than Marinol. (b) (4)

3. Physical manipulation of the Product is easier than with Marinol. Removing the formulation, either from the Product dispenser or extracting the sesame oil formulation from the capsules, would be the first step in physical manipulation for purposes of abuse. In vitro studies demonstrated that it is easier and more efficient to remove the dronabinol solution from the Product dispenser than to remove the sesame oil formulation from capsules. Although you did not conduct specific studies to show this difference, a loss of approximately 30 % recovered API was reported in the preparation of the sesame oil sample for the drying studies. As part of the drying studies, the content of one capsule of Marinol was taken up by syringe, and the amount of API recovered from the sample was measured. Although the sample was not subject to any further manipulation, a high percentage of the API was lost in the process. The loss of recovered API may be explained by the loss of the sesame oil formulation due to the adherence of the oil to any instrument used to handle the samples.

Insys Response

Approximately 30% loss was reported while using a syringe for removal of the capsule content from Marinol. Insys conducted additional studies where the capsule was simply cut open with scissors and the content was squeezed out. In trials using seven capsules, 93-97% of the content was recovered (see Report CH.0030). As demonstrated in the accompanying video, removing the capsule content from seven capsules takes less than 1 min. The resulting liquid does not require any further manipulation for abuse and the liquid from the capsule contains 3 to 12 times more dronabinol on an “mL to mL” basis than SYNDROS.

Therefore, physical manipulation of Dronabinol capsules to recover its liquid content is relatively as easy as SYNDROS oral solution. In the drying studies, the shortest duration for drying time for 2 mL of SYNDROS oral solution was 7 min when using a microwave. In 7 min all 60 capsules in a bottle of Marinol can be opened and the content recovered. Using 10 mg capsules, that would provide 465 mg dronabinol (based on at least 93% recovery of capsule

content) for abuse compared to 5 mg from SYNDROS oral solution in terms of total amount recovered by physical manipulation (see Table 1 below). These data suggest that Marinol capsules have greater potential for abuse than does SYNDROS.

Table 1 Comparison of Time to Recover Liquid from Syndros Bottle and Marinol Capsule Bottle by Drug Abuser

	Syndros Bottle	Marinol 2.5 mg Capsule Bottles	Marinol 5 mg Capsules Bottle	Marinol 10 mg Capsule Bottle
Content of Bottle	30 mL	60 Capsules	60 Capsules	60 Capsules
Total THC content per Bottle	150 mg	150 mg	300 mg	600 mg
Estimated time to remove liquid and THC Recovered from Capsules by abuser	About 150 mg	About 150 mg	About 300 mg	About 600 mg
Estimated Time for Recovering 150 mg THC		5.4 minutes	2.7 minutes	1.4 minutes
Approximate mg of THC per mL of liquid	5 mg	15 mg	30 mg	60 mg

CSS Response:

Your finding is not relevant. The 150 mg of dronabinol (bioequivalent to 176 mg of dronabinol as supplied in Marinol capsules) contained in SYNDROS are immediately available for consumption by an abuser. SYNDROS can be drunk quickly without any prior manipulation. You haven't performed a test to dispute the pleasant sweet alcoholic flavor.

4. The studies conducted with the Product are not convincing to demonstrate that it cannot be easily abused by inhalation (smoking and vaping). In vitro evaporation studies (drying studies) showed that the alcohol component of the Product is readily volatilized when exposed to minimal heat, affording concentrates that can be used for smoking or vaping or, as you state in your submission, used intranasally. However, you did not conduct smoking or vaping studies with these concentrated residues. Use of these concentrates was limited to the application of the residues to tobacco paper, and you did not use these concentrates to spike traditional tobacco cigarettes or in vaporization studies using e- cigarettes. The submitted studies explore the feasibility of abusing these concentrates through the intranasal mucosa; however, the intranasal route does not seem to be a common route of abuse of dronabinol. Moreover, your submitted smoking and vaping studies comparing the Product to Marinol capsules have major deficiencies.

Insys Response: Insys does not agree with the Agency's assertion that Insys' smoking and vaping studies have major deficiencies. As stated earlier, the Information Request dated December 30, 2015, contained a request to conduct studies to assess the feasibility of vaping the oral solution and the contents of the Marinol capsules, as well as the reconstituted product extracts using a representative electronic cigarette device (E-cigs) as well as using other vaporizers such as the Volcano. There are no standards for conducting these types of trials and

Insys had one month to research the available devices on the market for abusers, obtain the devices, familiarize yourselves with their use, determine how to conduct these trials, conduct the studies, and provide the Agency with the results. Insys tried to replicate the conditions that an actual abuser would use and not those carefully developed conditions of a research laboratory for vaporizing.

4. a. You evaluated the feasibility of smoking dronabinol by applying the dronabinol containing residue extracted from the products to tobacco rolling paper as a vehicle for smoking the residue. This method was demonstrated to be ineffective for the purpose of smoking dronabinol, because the tobacco paper rapidly turned to ash as it quickly combusted. However, this result is of limited utility since a modified strategy would likely provide a means of successful administration via the smoking route.

Insys Response: For an abuser the general criteria are to be able to manipulate any product with minimal efforts and within a reasonable time. If applying the product directly to the tobacco rolling paper and then smoking does not work, then the modified strategy for an abuser will be to use an actual cigarette to absorb product. These studies were also conducted and previously provided results demonstrated that only the sesame oil from Marinol capsules was successfully burned when combined with a tobacco cigarette. Both products would require considerable forethought and significant expenditures of time and effort to obtain similar results from buying marijuana, which doesn't seem like a reasonable assumption.

CSS response: You did not conduct appropriate studies to demonstrate that concentrates obtained by evaporation of your product cannot be smoked.

b. You evaluated the feasibility of using traditional cigarettes spiked either with the Product solution or the content of Marinol capsules, and you concluded that it was not possible to smoke either preparation. However, these studies, including the methods used to apply the extracted dronabinol to the cigarette and the conditions used to simulate smoking, were not adequately described. Also, there was no comparison using a tobacco cigarette alone with the same methods, in order to provide assurance that the methods had the potential to administer dronabinol by measuring nicotine administration for all samples.

Insys Response: The experimental details were described in the Report CHP12009. Both products were directly applied to a cigarette until the cigarette was saturated. The amount of product applied to the cigarette was recorded in the report. Product soaked cigarettes were then air dried. Time of drying was also recorded in the report. To simulate smoking, the method utilized was applying a vacuum at the end of the lighted cigarette and passing smoke through an ethanol solvent trap to trap dronabinol contained in the smoke. The method showed presence of dronabinol in the solvent trap when analyzed.

CSS Response: CSS's initial question was based on the review of the data found in Report CHP12009. You did not use a concentrate of the product when spiking the cigarettes and you did not include appropriate standards in your study.

c. You conducted studies to evaluate the amount of dronabinol that could be inhaled by vaporization of the dronabinol solution from the Product or by vaporization of the contents of Marinol capsules, using the Volcano vaporizer. Under your experimental conditions, the amount of vaporized dronabinol using the Volcano apparatus was low; however, your chosen experimental conditions may not have been optimal to achieve the highest levels of dronabinol vaporization. The studies conducted by Solowij et al., 2014, using the Volcano vaporizer and tetrahydrocannabinol (THC) samples applied to the Volcano Liquid Pad in ethanol demonstrate that up to 78 % of THC could be recovered at the same temperature of vaporization used in your vaporization studies. The discrepancy between your study results and the published data may be due to the manner in which samples were prepared and applied to vaporization pad, as well as the way the vapors were collected. Study results more aligned with published data could potentially have been achieved if formulation extracts taken in ethanol were loaded into the Volcano Liquid Pad, instead of the loading of the formulations without prior manipulation.

Insys Response: Insys reviewed the methodology used in Solowij et al., 2014 publication (BMC Pharmacology and Toxicology 2014, 15:58; A Protocol for the delivery of cannabidiol (CBD) and combined CBD and delta-9-tetrahydrocannabinol (THC) by vaporization). Researchers used several preliminary experiments to optimize the vaporization conditions as well as techniques to capture the active ingredient from vapors collected in the balloon. Ethanol was used simply to apply the active ingredient to the pad and was pre-evaporated prior to vaporization. Researchers also used multiple balloons to collect vapors. The careful methodology was developed so that it could be used in a future clinical trial to deliver consistent doses of CBD and THC to the subjects.

A survey of You-Tube videos on the internet showed that appearance of visible smoke that is collected in the plastic bag is the clue for a user that the marijuana has vaporized when a Volcano vaporizer is used. In Insys' experiments, SYNDROS was directly applied to the liquid pad and vaporized. The vapors generated were directly passed through the ethanol solvent trap to trap dronabinol. Visual observation indicated that for both SYNDROS oral solution and Dronabinol capsules, when applied directly to the solvent trap, the smoke did not appear for four to five minutes, presumably due to the formulation components contained in SYNDROS oral solution and sesame oil in dronabinol capsules.

Insys conducted additional experiments where 1 mL of SYNDROS oral solution and 1 mL capsule content from 10 mg capsules were vaporized directly using a Volcano vaporizer. SYNDROS oral solution yielded an average of 0.162 mg dronabinol based on two trials. Marinol capsules content yielded an average of 0.080 mg dronabinol following two trials (see Report CH.0029 for further details).

If the carefully developed techniques used in the Solowij publication are used on both products after extraction, the fact that approximately 51 mg of dronabinol can be extracted from 1 mL of Dronabinol capsule content versus 4.75 mg of dronabinol extracted from 1 mL of SYNDROS oral solution makes capsules more likely to be abused using the volcano vaporizer and Solowij techniques. However, these studies demonstrate that the use of the Volcano is not a viable

method of abusing either SYNDROS or Dronabinol capsules because very small amounts of dronabinol are recovered in 25-30 minutes of vaporization.

CSS Response:

You have not addressed CSS's original question. You have not conducted studies to prove that extracts of your formulation can be taken in alcohol and vaporized using the Volcano vaporizer. Your assessment that an abuser will limit the extraction and preparation of dronabinol oil for smoking purposes to the use of 1 mL of SYNDROS is not supported by data. In order to prepare extracts of marijuana for smoking, abusers report going through the extremes of conducting liquid gas extraction utilizing flammable low boiling hydrocarbon gases such as butane and propane (Raber, Elzinga, & Kaplan, 2015). In addition, published data in peer review journals are available in the public domain and there is no way to control who has access to it.

d. You conducted studies to assess the feasibility of vaping the dronabinol solution from the Product versus vaping the contents of Marinol capsules using a specific type of electronic cigarette. These studies showed a low recovery of dronabinol from vaporization of the non-manipulated samples of the formulations or from extracts in ethanol under the experimental conditions chosen. However, these studies are not conclusive because no validation of the conditions chosen including the type of e-cigarette selected, the temperature and power of the vaporizer, the solvent selected in the preparation of the samples, the smoking procedure selected, and the smoking machine used was not provided or conducted.

Insys Response: On December 30, 2015, Insys received a Request for Information that asked “to conduct studies to assess feasibility of vaping oral solution and the contents of the Marinol capsules using representative electronic cigarette devices (E-cigs)”. There are no Guidance documents concerning the conduct of these studies. Based on this request, Insys evaluated several commonly used E-cigs for their ability to produce visible smoke. Appearance of visible smoke is how E-cigs are checked by the user for vaping. That is how an abuser will assess if an E-cig is working. This was also confirmed by conversations with regular E-cig users at the local vaping supply stores. The E-cigs evaluated were Subox Mini, Cannastick, Pinnacle Pro, Ambassador Kit V4 and Vapresso. E-cigs with cotton and silica wick did not work as the atomizers burned due to over-heating when used for these two products. These types of E-cigs would be unsuitable for an abuser as atomizers would have to be replaced frequently adding to the cost of using such a device. Vapresso was used in all the experiments because it produced smoke for both products. Wattage used for the experiments was recorded in the reports. For simulation of smoking, the E-cig was attached to a vacuum source and smoke was passed through an ethanol solvent trap to trap dronabinol in ethanol. This procedure was described in the report. Validation of the method was addressed by the screening of several E-cigs to choose the one that allowed for visual confirmation through the appearance of smoke with these products. Not all the E-cigs have wattage control. The ones that provided wattage control, wattage was used where atomizers did not short out after each use and where the units did not overheat. The Vapresso brand of E-cig uses a ceramic wick that was found to be most suitable for use with these products. The wattage was selected based on the E-cig generating consistent smoke for vaping from each product and at the same time not overheat.

Insys has conducted additional studies using the Vapresso E-cig with 1 mL of SYNDROS oral solution and 1 mL of Dronabinol capsule content from 10 mg capsules in a head-to-head comparison. From 1 mL of SYNDROS oral solution, 0.088 mg of dronabinol was recovered as the average of two trials (see Report CH.0029). From 1 mL of Dronabinol capsule content 2.44 mg of dronabinol was recovered as the average of two trials. This experiment demonstrated that capsule content from 10 mg capsules can deliver a dose 27 times higher of dronabinol compared to SYNDROS oral solution when used directly in an E-cig.

The results from these additional studies, combined with the results from the earlier trials, confirm that Marinol capsules have greater abuse potential than SYNDROS oral solution.

CSS Response:

Your study did not include a THC standard to validate the conditions of the study, and does not address the feasibility of using extracts or concentrates of SYNDROS for the purpose of abuse. See response to question 4. b regarding the limited scope of comparing SYNDROS to Marinol capsules in mL per mL basis.

5. As a sweet alcoholic solution of dronabinol, the Product is formulated such that it would be appealing to users and abusers. The large content of dronabinol in the Product and the composition of the formulation (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic sweetened solution), and bioavailability of the solution relative to the Marinol capsule (150 mg bioequivalent to 176 mg of dronabinol capsules) adds to the abuse potential of the formulation and to the risk of adverse outcomes and of unintentional overdose from abuse when taken through the oral route as CNS adverse reactions are dose-related. In addition, the perceived risks associated with drinking 30 mL of an alcoholic solution may be different than the perception of the risks associated with ingesting 70 Marinol 2.5 mg capsules or 17 Marinol 10 mg capsules, though the bioequivalent amount of dronabinol taken in both situations may be the same.

Insys Response: The perception that the risk of overdose from ingestion of liquid preparations is different from that of the unintentional overdose of a solid dosage form appears speculative in the absence of data to support such a premise. Abuse is often intentional and not unintentional and in the case of SYNDROS, the likability and safety were demonstrated to be comparable to Marinol (Study INS-13-017) at supratherapeutic doses 3-fold higher than the typical therapeutic dose. Overdosage also depends upon product characteristics of the supplied product. Specifically, the bottle containing SYNDROS has a total amount of dronabinol of 150mg. In contrast a 60 count bottle of Marinol 10 mg capsules that has a total amount of dronabinol of 600mg. The 4-fold lower total quantity of dronabinol confers a much lower risk due to unintentional (or intentional) overdose for individuals likely to abuse SYNDROS. Consequently, dose related adverse effects due to overdose would be expected to be greater with the 600 mg of Marinol accessed from a single 60 count bottle of 10 mg capsules in contrast to the 4-fold lower total dose of 150 mg accessed from a single bottle of SYNDROS. Thus, the risk of overdose associated with Marinol is higher than that associated with SYNDROS.

CSS Response:

We agree with your statement that overdosage depends upon the product characteristics of the supplied product; however we don't agree that the risk of overdose and the occurrence of serious psychiatric adverse events in the context of abuse are higher with Marinol than with SYNDROS. Your product provides 150 mg of dronabinol (bioequivalent to 176 mg of dronabinol in sesame oil). Thus, to consume 176 mg of Marinol an individual would have to consume 70 Marinol 2.5 mg capsules, 35 capsules of Marinol 5 mg capsules or 17-18 Marinol 10 mg capsules. While one may drink the 30 mL of your product without realizing that he or she is consuming a large amount of dronabinol, the individual will certainly have to make a conscious decision to ingest such a large number of capsules. Under the latter circumstances overdose will be intentional.

Several cases of delta-9-THC unintentional overdoses from eating delta-9-THC- containing products have been reported in the peer review literature. These cases required hospitalization and treatment, and one case resulted in the death of the individual (Chaudry et al., 1991; Hancock-Allen et al., 2015; Hudak et al., 2015; Mehrpour et al., 2012; Nicks, 2014; Sapienza, 2006; Weiss, 2015)

6. The Product mediates a greater array of psychiatric adverse events (AEs). In the human abuse potential study (Clinical Trial INS-13-017) there were more psychiatric AEs (euphoric mood, thinking abnormal, and hypervigilance) following administration of the Product compared with administration of Marinol, when the same dose amounts are administered. This was true for both 10 mg and 30 mg administered doses.

Insys Response: It is Insys' assessment that there are no differences in the incidences of these adverse events between Marinol and SYNDROS oral solution when compared at the same dose level (10 mg or 30 mg) as outlined in Table 2 with p-values ranging from 0.25 to > 0.99 for each of the AE comparisons for "All Marinol" compared to "All Dronabinol." For example, a comparable rate of AEs was noted with euphoric mood occurring at 68.6% and 72.2% for Marinol and the SYNDROS oral solution, respectively at the 10mg dose. Similarly, a comparable rate of AEs are noted for euphoric mood at the supra-therapeutic dose of 30 mg with AEs rates of 81.1% and 87.5% in the Marinol and SYNDROS oral solution treatments, respectively. The adverse event of thinking abnormal generally occurred at a very low incidence of 1 and 2 subjects following SYNDROS oral solution 10 and 30 mg, compared to 0 for both Marinol doses. Whereas hypervigilance occurred in 1 subject following Marinol 10 mg (compared to 0 subjects following SYNDROS oral solution 10 mg). In contrast, 2 subjects experienced hypervigilance following SYNDROS oral solution 30 mg compared to 0 subjects following Marinol 30 mg. The adverse events observed are very similar between treatments and generally occur at low rates. In such circumstances, the data obtained from Visual Analogue Scale (VAS) measurements can be very helpful in interpreting these relevant safety events. In this study, the VAS scales for High showed similar Emax scores for Marinol and SYNDROS, although the means were slightly higher for SYNDROS, with no statistical significance. In the totality of the data from this study, it shows that both substances were very similar in the

responses elicited to measures related to abuse potential. Overall, the incidence of the adverse events in Table 2 were comparable between the treatment administered at the same dose level (Marinol 10 mg vs. SYNDROS oral solution 10 mg and Marinol 30 mg vs. SYNDROS oral solution 30 mg). Comparable results are also observed for the psychiatric AEs across all studies conducted as depicted in Table 3 below.

In summary, the totality of the data suggests a comparable rate of psychiatric AEs for both SYNDROS and Marinol.

Table 2. Treatment-Emergent AEs for Psychiatric Disorders (euphoric mood, thinking abnormal and hypervigilance) Clinical Study Report INS-13-017 (Human Abuse Liability Study)

Preferred Term	Placebo (N=39)	Marinol (10mg) (N=35)	Marinol (30mg) (N=37)	Dronabinol (10mg) (N=36)	Dronabinol (30mg) (N=40)	All Marinol (N=72)	All Dronabinol (N=76)	p-value ²
Euphoric Mood	3 (7.7)	24 (68.6)	30 (81.1)	26 (72.2)	35 (87.5)	54 (75%)	61 (80%)	p=0.55
Thinking abnormal	0	0	0	1 (2.8)	2 (5.0)	0	3	p=0.25
hypervigilance	0	1 (2.9)	0	0	2 (5.0)	1	2	p>0.99

Table 3. Treatment-Emergent AEs for Psychiatric Disorders (euphoric mood, thinking abnormal and hypervigilance) from Pharmacokinetic Studies^a

Preferred Term	Study INS-08-008			Study INS-10-012		Study INS-12-015		Study INS004-15-059		
	SYNDROS 10 mg	Dronabinol Oral Solution 10 mg ^b	Marinol 10 mg	SYNDROS 5 mg	Marinol 10 mg	SYNDROS 4.25 mg	Marinol 5 mg	SYNDROS 4.25 mg Fed	Marinol 5 mg Fed	Marinol 5 mg Fasted
	N=18	N=18	N=18	N=169	N=171	N=104	N=104	N=52	N=54	N=53
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Euphoric Mood	0	0	0	1 (0.6)	0	0	1(1.0)	2 (3.8)	0	1 (1.9)
Thinking Abnormal	0	0	0	0	0	0	0	0	0	0
Hyper vigilance	0	0	0	0	0	0	0	0	0	0

^aIntegrated Summary of Safety, NDA 205525

^bPrevious test formulation of Dronabinol Oral Solution

CSS Response:

We agree that abuse associated adverse events (AEs) reported between SYNDROS and equivalent doses of Marinol are similar (the differences were not statistically significant). SYNDROS, however, consistently shows a greater number of these AEs, at equivalent doses, as well as some that were not seen at all with Marinol. A greater number of subjects experienced a euphoric mood with SYNDROS compared with Marinol at both 10 mg and 30 mg (your Table 2). Similarly, again in Table 2, there were no reports of thinking abnormal with either dose of Marinol while there were a small number with SYNDROS, more at 30 mg than 10 mg.

The pharmacodynamic results from your HAPS, Visual Analog Scale (VAS), consistently show greater drug abuser preference with SYNDROS as compared with Marinol. The High VAS mean Emax of Marinol 10 mg/SYNDROS 10 mg was 60.5/67.3 while Marinol 30mg/SYNDROS 30 mg was 85.8/88.8. Similarly, the Stoned VAS mean Emax of Marinol 10 mg/SYNDROS 10 mg was 53.0/55.9 while Marinol 30 mg/SYNDROS 30 mg was 81.1/84.4. Finally, the Drug Liking VAS mean Emax of Marinol 10 mg/SYNDROS 10 mg was 78.1/81.4 while Marinol 30 mg/SYNDROS 30 mg was 89.0/91.7. Although not statistically significant, SYNDROS consistently shows a trend of more AEs associated with abuse and greater drug abuser preference than Marinol.

7. The human abuse potential study (Clinical Trial INS-13-017) demonstrated that the Product has an abuse potential comparable to that of Marinol in recreational cannabis users, when taken as prescribed, following administration of single doses no greater than 30 mg. This study did not evaluate multiple dosing effects and drug liking at higher doses. The abuse potential of the Product relative to that of Marinol when administered via the sublingual route was not addressed in human abuse potential studies. Both alcohol and dronabinol are readily absorbed sublingually, raising the potential for another abuseable route of administration of the Product which would not be possible with Marinol.

Insys responses to each item in Question #7 are discussed below. The Agency comments from Questions #7 are presented in italic font and Insys' response is in regular font. Agency Comment: *The human abuse potential study (Clinical Trial INS-13-017) demonstrated that the Product has an abuse potential comparable to that of Marinol in recreational cannabis users, when taken as prescribed, following administration of single doses no greater than 30 mg. This study did not evaluate multiple dosing effects and drug liking at higher doses.*

Insys Response: The doses of SYNDROS were selected based on doses previously demonstrated to produce significant effects on measures of drug liking in non-dependent recreational drug users. Since the objective of the study was to compare dronabinol in oral solution to its active control (Marinol), it was deemed most appropriate to directly compare the same doses of each drug within a range of doses that have been previously shown to create positive effects on subjective measures. Previous studies have used 10 to 20 mg dronabinol and have shown significant effects on measures of abuse potential (Kirk et al 1998; Hart et al 2002; Schoedel et al 2012). In this study, two doses were used that would be expected to produce positive subjective effects in the study population, i.e., 10 and 30 mg. A higher dose of 30 mg was selected to represent a supra-therapeutic dose that would be well tolerated in the study population.

Human abuse potential studies are designed to evaluate single-dose administration, and therefore, these studies do not evaluate multiple dosing effects. In addition, this study was designed in accordance to the recommendations of the FDA Guidance for Industry which clearly states that single-dose administrations are evaluated. Specifically, the Guidance states the following:

The human abuse study measures repeated single-dose administrations over a period of time, determined by the time course of the drug's effects. (FDA Guidance for Industry: Assessment of Abuse Potential of Drugs, Draft Guidance, January 2010, p.14).

Also, it is important to note that each subject in Study INS-13-017 received repeated single-dose administrations – a total of five administrations of drug/placebo (SYNDROS placebo).

In August 2013, the study protocol INS-13-017 was submitted to the FDA for review and comment. In December 2013, the Agency provided Insys with a Written Response outlining the following recommendation on dosing:

The purpose of the study is to evaluate the abuse potential of Dronabinol Oral Solution in comparison to Marinol, a marketed Schedule III substance. Thus, the doses of your product that are tested should be equivalent in actual milligram (mg) amounts to the doses of Marinol that will be used as the positive control. The protocol should be revised so that the doses of Dronabinol Oral Solution are 10 and 30 mg, since the doses of Marinol that will be tested are 10 and 30 mg. (IND75228, FDA Meeting Request—Written Response, December 2013).

Based on these written recommendations, Insys incorporated the Agency's comments and proceeded with the study. No comment or recommendation was provided on selecting a dose higher than 30 mg. Also, it is important to note that the Agency did not disagree on the single-dose administration outlined in the protocol and did not recommend that a multiple-dose administration study design should be chosen. Thus, the results from this study do support Insys' position that SYNDROS is no more likely to be abused than Marinol.

Agency Comment: The abuse potential of the Product relative to that of Marinol when administered via the sublingual route was not addressed in human abuse potential studies. Both alcohol and dronabinol are readily absorbed sublingually, raising the potential for another abuseable route of administration of the Product which would not be possible with Marinol.

Insys Response: While drugs can certainly be abused by other routes, the primary objective of the current study was to evaluate the abuse potential of SYNDROS oral solution when ingested. Absorption while in the mouth can in part be mediated by sublingual absorption as well as by GI absorption, particularly because a portion of the drug with saliva is swallowed. Generally, sublingual administration is also mediated more readily when tablets or solid dosage forms are kept under the tongue compared to a liquid, as the dosage form remains intact long enough to be held under the tongue. With an oral solution, the length of time that the solution could be held under the tongue without swallowing would be comparably shorter than that of a solid dosage form. With attempts to hold the solution under the tongue, it is expected that a large proportion of the solution would be inevitably swallowed and thereby absorbed by the stomach/GI. The maximum amount of volume that can be comfortably retained in the sublingual pocket is reported to be in the range of about 0.4 mL. In this case, dronabinol was administered as an oral solution directly into the mouth using a syringe. Attempts to hold a solution under the tongue would be expected to be in short duration and highly variable with the degree of swallowing and time to first swallow. Sativex, an oromucosal spray containing THC and CBD, is marketed in the

United Kingdom and Canada by G Pharmaceuticals. Each mL of Sativex contains 27 mg of dronabinol and 25 mg of CBD in 50 % ethanol and (b) (4) % propylene glycol. It should be noted that even with smaller volumes of highly concentrated alcohol spray (approximately 5-fold higher concentration than SYNDROS) administered oromucosally, the Tmax for THC is 1 hour (Sativex, Summary of Product Characteristics, May 20, 2015; GW Pharma). Consequently, the sublingual route of administration presents a much lower potential for abuse for SYNDROS relative to Marinol, when compared to the current preferred method, smoking.

CSS Response:

The preclinical and clinical abuse potential studies recommended in the Agency's Guidance on abuse potential assessment are studies recommended for use in evaluating the abuse potential of new drugs. These few studies (animal drug discrimination, self administration, and dependency studies and the human abuse potential study), which are unique for assessing abuse potential, need to be evaluated as one part of the usual safety and efficacy and chemistry studies used for assessing new drugs. We agree with you that the results of your Human Abuse Potential Study (HAPS), when viewed in isolation and not in the context of the overall properties of the drug, may have confused Insys interpretation that your drug product (SYNDROS) is no more likely to be abused than Marinol. Although the HAPS provides important information about the abuse potential of a drug, it does not mitigate the in vitro evaluations of your product which suggest its greater abuse potential. When these clinical results are combined with the in vitro studies, we find that SYNDROS has greater abuse potential. As you know, the HAPS represents individual responses to single dose administrations of a range of doses of your drug relative to a positive control. It does not give us abuse related information from multiple dosing of your drug product over a period of days or factor in abuse by alternative routes of administration or aberrant behaviors.

Our viewpoint on the sublingual route of abuse is addressed in CSS's response to Question #2.

Carton and Container submitted March 18, 2016:

A. Carton and Container

1. We recommend revising the storage statement to read as follows, “Before use: Must be refrigerated, store at...”, to increase clarity and prominence of this important information and minimize the risk of storage information being misinterpreted or overlooked.
2. We recommend revising the statement “Once opened the bottle can be stored at room temperature,” to read as follows: “Once opened, the bottle can be stored at room temperature. Date of first opening __/__/__/. Discard unused portion 28 days after first opening.”, in bold font. The “__/__/__/ _” statement will alert users to write a complete date (month/day/year) on the container and carton labeling.
3. We recommend adding the following statement to the Principal Display Panel (PDP) in prominent font type: “Dispense in original container with oral syringe for administration.” If more space is required, relocate the net quantity and Rx Only statement to the bottom of the PDP.

B. Carton Labeling Only

1. Remove from the left side panel, (b) (4), as this is also available on the back panel, to reduce clutter and redundant information.
2. Remove the statement (b) (4) from the side panel, due to Recommendation A.3.
3. Relocate the storage information to a side panel to reduce clutter and ensure that this information is not overlooked.
4. Add to the left side panel, as a separate bullet, the following: “Pharmacists: Provide patients with dosing instructions in milliliters (mL) and round dose to nearest 0.1 mL increment.”

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

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/s/

MAUREEN D DEWEY
04/25/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205525

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Insys Development Company, Inc.
Attention: Steven Sherman
Vice President, Regulatory Affairs
1333 South Spectrum Boulevard
Chandler, AZ 85286

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SYNDROS (dronabinol oral solution) 0.85mL/4.25mg.

On March 10, 2016, we received your March 10, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 1, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 23, 2016.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA

Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BRIAN K STRONGIN
03/22/2016

From: [Dewey, Maureen](#)
To: [Stephen Sherman](#)
Cc: [Dewey, Maureen](#)
Subject: RE: NDA 205525 Tcon Follow-Up
Date: Wednesday, March 16, 2016 5:27:59 PM

Mr. Sherman,

It appears we were experiencing technical difficulties, I am re-sending this email with minor editorial changes.

As discussed on the teleconference on March 15, 2016, Insys will submit to the FDA a side-by-side comparison table of the performance and compatibility of the new oral dispensing syringe.

Specifically for the biocompatibility and drug compatibility testing, please provide the following for the new oral dispensing syringe:

1. A table comparing the material formulation of the device components for the original syringe (that was submitted and reviewed under NDA 205525 (DMF# (b) (4))) to those of the newly proposed syringe that you plan to supply under the NDA 205525.

2. A certification statement (see below). Please note that to state that the materials are identical, the raw materials should come from the same supplier including all additives and processing agents.

The [polymer/metal/ceramic/composite name] [component names] of the [proposed device] are identical to the [component names] of the [device that is currently under review under the NDA 205525] in formulation, processing, and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.)."

Please confirm receipt and feel free to contact me if you have any questions.

Regards,

Maureen Dewey, MPH
Senior Regulatory Project Manager | DGIEP | ODE III | OND | CDER | FDA | 301.796.0845 | FAX 301.796.9904
maureen.dewey@fda.hhs.gov

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MAUREEN D DEWEY
03/17/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 2, 2016; 4:00 – 5:00 PM
Application Number: NDA 205525
Product Name: dronabinol oral solution
Sponsor/Applicant Name: Insys Development Company, Inc.
Call Information: (b) (4) Conference Code: (b) (4)
Subject: Scheduling Decision

FDA Participants:

ODE III

Julie Beitz, M.D., Director

Maria Walsh, R.N., M.S., ADRA

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Andrew Mulberg, M.D., Deputy Director, DGIEP

Joette Meyer, Pharm.D., Associate Director for Labeling

Kelly Richards, Regulatory Project Manager, DGIEP

Controlled Substance Staff (CSS)

Michael Klein, Ph.D., Director

Silvia Calderon, Medical Officer,

Martin Rusinowitz, M.D., Medical Officer

Dominic Chiapperino, Ph.D., Regulatory and Liaison Team Leader

Sponsor/Applicant Participants:

Insys Development Company, Inc.

John Kapoor, Ph.D., Executive Chairman, President & CEO

Ramesh Acharya, Executive Vice President, Scientific Operations

Neha Parikh, Vice President, Clinical Operations,

Stephen Sherman, Vice President, Regulatory Affairs

1.0 BACKGROUND:

NDA 205525 is a 505(b)(2) application for dronabinol oral solution (4.25 mg/0.85 ml). The product is co-packaged with a dosing syringe.

Dronabinol oral solution is a new formulation of dronabinol, and contains synthetic delta-9-tetrahydrocannabinol (delta-9-THC).

The applicant is relying for approval on the FDA's finding of safety and effectiveness for Marinol (dronabinol capsules) approved on May 31, 1985. The applicant proposes the same indications as Marinol, which are as follows:

- 1) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and
- 2) anorexia associated with weight loss in patients with AIDS.

On June 1, 2015 the application was submitted and received after a refuse to file decision was issued on October 10, 2014.

The purpose of the telecon is to inform Insys that we disagree with their scheduling recommendation for Schedule III.

- Applicant invited to provide any comments on the CSS recommendation.
- Inform the applicant that if they disagree with the recommendation, they may submit a dispute resolution to Dr. Throckmorton. The dispute resolution must be filed within 7 days of the telecom, due to the time constraints to get a scheduling action through FDA, NIDA, OCC and HHS by the PDUFA date.

2.0 DISCUSSION:

Reasons for Schedule II recommendation:

1. The Product (Dronabinol Oral Solution) is currently listed in Schedule I of the CSA. If approved for marketing, in order for the Product to be legally marketed, it must be rescheduled to a lower schedule of the CSA. The abuse liability properties of Marinol (Schedule III), the only other approved dronabinol-containing drug product, are used for comparison with the Product. Marinol, as opposed to Dronabinol Oral Solution, is formulated (dissolved in sesame oil in a gelatin capsule) in a manner that vitiates the abuse liability of the API, dronabinol.
2. The Product is easily manipulated for abuse by inhalation and oral routes.
3. The formulation of the Product has important differences from Marinol that facilitate product manipulation. Product has inherent PK/PD properties that make it potentially more abuseable than Marinol.
4. Physical manipulation of the Product is easier than that of Marinol.
5. The API in the Product can more easily be extracted than from Marinol.
6. The Product can easily be abused by inhalation (smoking and vaping).
7. Sponsor's smoking studies showing Product similarity to Marinol capsules has major deficiencies.
8. As a sweet alcoholic solution of dronabinol, the Product is formulated to be appealing to users and abusers.
9. The Product mediates a greater array of psychiatric AEs.
10. The risk of overdose with dronabinol products is described in the Marinol and Dronabinol Oral solution labels.
11. The human abuse potential (Clinical Trial INS-13-017) study confirmed that Dronabinol Oral Solution has an abuse potential comparable to that of Marinol in recreational

cannabis users *when taken as prescribed, following administration of single doses no greater than 30 mg.*

12. The abuse potential of the Dronabinol Oral Solution relative to that of Marinol when administered via the sublingual route was not addressed in human abuse potential studies.
13. As stated in the Marinol label and in the Dronabinol Oral Solution label, CNS adverse reactions are dose-related, increasing in frequency with higher doses, and subject to inter-patient variability.
14. In the State of Colorado, where there is a wide variety of products infused with delta-9-THC, policymakers have considered imposing caps on all recreational edibles at 10 mg delta-9-THC (one tenth of the currently allowed levels) (National Conference of State Legislatures, 2015).
15. Based upon the results from the *in vitro* studies discussed in this review, the large quantity of dronabinol in the supplied Product, its pharmacokinetics when taken orally, and principle contribution to marijuana psychoactivity (Schedule I), the abuse potential of the Dronabinol Oral Solution is higher than the abuse potential of drugs in Schedule III.

3.0 ACTION ITEMS:

Insys disagreed with FDA's Schedule II recommendation for their Product. Insys indicated they would consider submitting additional data to the application to support the acceptability of their previously proposed Schedule III recommendation.

Insys requested a written summary of FDA's reasons for Schedule II recommendation in order to develop a potential appeal to Dr. Throckmorton for dispute resolution. FDA agreed to provide a written summary of the teleconference as soon as possible.

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/s/

MAUREEN D DEWEY
03/10/2016



NDA 205525

INFORMATION REQUEST

Insys Development Company, Inc.
Attention: Stephen Sherman
Vice President, Regulatory Affairs
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ 85286

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for dronabinol oral solution.

We also refer to the teleconference between you and FDA's Controlled Substance Staff (CSS) and the Division of Gastroenterology and Inborn Errors Products (DGIEP) held on March 2, 2016, during which you were informed that FDA had determined your drug currently under review will be recommended for rescheduling from Schedule I to Schedule II of the Controlled Substances Act (CSA), instead of Schedule III as Insys proposed.

Generally, we have concluded that dronabinol oral solution (the Product) is easily manipulated for abuse by inhalation and oral routes. The in vitro study data demonstrate that the Product can be manipulated to afford highly concentrated dronabinol extracts that can be abused by the inhalation route. Additionally, the Product may serve as an easily accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) for purposes of oral abuse. Therefore, we have concluded that the Product has a greater potential for abuse than Marinol capsules and presents a greater risk of unintentional overdose if abused.

As you requested, we are providing the reasons for our determination listed below for your consideration when preparing your appeal, which is due no later than March 9, 2016.

1. The formulation of the Product has important differences from Marinol that facilitate product manipulation. Data from submitted in vitro studies do not support your claim that the Product and Marinol capsules are chemically similar. The Product, in comparison to Marinol capsules, can be easily concentrated by evaporation when exposed to minimal heat. In addition, a higher percentage of dronabinol is extracted from the Product with methylene chloride than from Marinol capsules (using the best solvent for extraction that

you identified). Methylene chloride extracted on average over 85 % of the API from the Product solution, while on average 65 % of API was extracted from the Marinol capsules in ethanol (an efficient extraction solvent used with Marinol). You concluded that extraction of the API from the Product and from dronabinol capsules is feasible. You further concluded that the extraction of the API from the Product is not more efficient or that it would not afford larger quantities of the API than the extraction from Marinol capsules, based on the assumption that a high volume of methylene chloride would have to be used to recover large quantities of dronabinol from the oral solution and that it will take longer to evaporate this solvent. However, the use of higher volumes of the solution and of extraction solvents does not impede the ability to extract larger amounts of dronabinol from the oral solution. In some instances, the use of larger volumes may actually increase the efficiency of the extraction by decreasing the losses that result from working with smaller extraction samples. Overall, in vitro manipulation studies demonstrate that the Product can be successfully manipulated to afford highly concentrated extracts in solvents that can be easily evaporated to give high content dronabinol residues that can be abused by smoking or through other routes of abuse.

2. The Product has inherent PK/PD properties that make it potentially more abuseable than Marinol. Although the Product and Marinol capsules can both be abused by oral ingestion, the Product may serve as an easily accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) for purposes of abuse. Additionally, and not addressed in your submission, the Product can be taken sublingually and absorbed bypassing oral ingestion. This raises the potential for another abuseable route of administration of high doses of dronabinol at levels that are not practically achievable with Marinol.
3. Physical manipulation of the Product is easier than with Marinol. Removing the formulation, either from the Product dispenser or extracting the sesame oil formulation from the capsules, would be the first step in physical manipulation for purposes of abuse. In vitro studies demonstrated that it is easier and more efficient to remove the dronabinol solution from the Product dispenser than to remove the sesame oil formulation from capsules. Although you did not conduct specific studies to show this difference, a loss of approximately 30 % recovered API was reported in the preparation of the sesame oil sample for the drying studies. As part of the drying studies, the content of one capsule of Marinol was taken up by syringe, and the amount of API recovered from the sample was measured. Although the sample was not subject to any further manipulation, a high percentage of the API was lost in the process. The loss of recovered API may be explained by the loss of the sesame oil formulation due to the adherence of the oil to any instrument used to handle the samples.
4. The studies conducted with the Product are not convincing to demonstrate that it cannot be easily abused by inhalation (smoking and vaping). In vitro evaporation studies (drying studies) showed that the alcohol component of the Product is readily volatilized when exposed to minimal heat, affording concentrates that can be used for smoking or vaping or, as you state in your submission, used intranasally. However, you did not conduct smoking or vaping studies with these concentrated residues. Use of these concentrates

was limited to the application of the residues to tobacco paper, and you did not use these concentrates to spike traditional tobacco cigarettes or in vaporization studies using e-cigarettes. The submitted studies explore the feasibility of abusing these concentrates through the intranasal mucosa; however, the intranasal route does not seem to be a common route of abuse of dronabinol. Moreover, your submitted smoking and vaping studies comparing the Product to Marinol capsules have major deficiencies.

- a. You evaluated the feasibility of smoking dronabinol by applying the dronabinol-containing residue extracted from the products to tobacco rolling paper as a vehicle for smoking the residue. This method was demonstrated to be ineffective for the purpose of smoking dronabinol, because the tobacco paper rapidly turned to ash as it quickly combusted. However, this result is of limited utility since a modified strategy would likely provide a means of successful administration via the smoking route.
- b. You evaluated the feasibility of using traditional cigarettes spiked either with the Product solution or the content of Marinol capsules, and you concluded that it was not possible to smoke either preparation. However, these studies, including the methods used to apply the extracted dronabinol to the cigarette and the conditions used to simulate smoking, were not adequately described. Also, there was no comparison using a tobacco cigarette alone with the same methods, in order to provide assurance that the methods had the potential to administer dronabinol by measuring nicotine administration for all samples.
- c. You conducted studies to evaluate the amount of dronabinol that could be inhaled by vaporization of the dronabinol solution from the Product or by vaporization of the contents of Marinol capsules, using the Volcano vaporizer. Under your experimental conditions, the amount of vaporized dronabinol using the Volcano apparatus was low; however, your chosen experimental conditions may not have been optimal to achieve the highest levels of dronabinol vaporization. The studies conducted by Solowij et al., 2014, using the Volcano vaporizer and tetrahydrocannabinol (THC) samples applied to the Volcano Liquid Pad in ethanol demonstrate that up to 78 % of THC could be recovered at the same temperature of vaporization used in your vaporization studies. The discrepancy between your study results and the published data may be due to the manner in which samples were prepared and applied to vaporization pad, as well as the way the vapors were collected. Study results more aligned with published data could potentially have been achieved if formulation extracts taken in ethanol were loaded into the Volcano Liquid Pad, instead of the loading of the formulations without prior manipulation.
- d. You conducted studies to assess the feasibility of vaping the dronabinol solution from the Product versus vaping the contents of Marinol capsules using a specific type of electronic cigarette. These studies showed a low recovery of dronabinol from vaporization of the non-manipulated samples of the formulations or from extracts in ethanol under the experimental conditions chosen. However, these

studies are not conclusive because no validation of the conditions chosen including the type of e-cigarette selected, the temperature and power of the vaporizer, the solvent selected in the preparation of the samples, the smoking procedure selected, and the smoking machine used was not provided or conducted.

5. As a sweet alcoholic solution of dronabinol, the Product is formulated such that it would be appealing to users and abusers. The large content of dronabinol in the Product and the composition of the formulation (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic sweetened solution), and bioavailability of the solution relative to the Marinol capsule (150 mg bioequivalent to 176 mg of dronabinol capsules) adds to the abuse potential of the formulation and to the risk of adverse outcomes and of unintentional overdose from abuse when taken through the oral route as CNS adverse reactions are dose-related. In addition, the perceived risks associated with drinking 30 mL of an alcoholic solution may be different than the perception of the risks associated with ingesting 70 Marinol 2.5 mg capsules or 17 Marinol 10 mg capsules, though the bioequivalent amount of dronabinol taken in both situations may be the same.
6. The Product mediates a greater array of psychiatric adverse events (AEs). In the human abuse potential study (Clinical Trial INS-13-017) there were more psychiatric AEs (euphoric mood, thinking abnormal, and hypervigilance) following administration of the Product compared with administration of Marinol, when the same dose amounts are administered. This was true for both 10 mg and 30 mg administered doses.
7. The human abuse potential study (Clinical Trial INS-13-017) demonstrated that the Product has an abuse potential comparable to that of Marinol in recreational cannabis users, *when taken as prescribed, following administration of single doses no greater than 30 mg*. This study did not evaluate multiple dosing effects and drug liking at higher doses.

The abuse potential of the Product relative to that of Marinol when administered via the sublingual route was not addressed in human abuse potential studies. Both alcohol and dronabinol are readily absorbed sublingually, raising the potential for another abuseable route of administration of the Product which would not be possible with Marinol.

If you have any questions, please contact Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, MD, FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
03/04/2016

PeRC Meeting Minutes
February 3, 2016

PeRC Members Attending:

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Gil Burckart

Thomas Smith

Daiva Shetty

Gettie Audain

Meshaun Payne

Dianne Murphy

Adrienne Hornatko-Munoz

Michelle Roth-Kline (Did not review

NON RESPONSIVE

)

Rosemary Addy

Maura Oleary (Reviewed

NON RESPONSIVE

)

Wiley Chambers

Shrikant Pagay

Belinda Hayes (Did not review

NON RESPONSIVE

Syndros,

NON RESPONSIVE

)

Lisa Faulcon

Lili Mulugeta

Freda Cooner

Barbara Buch

Agenda

NON RESPONSIVE

11:40	NDA 205525	Syndros (dronabinol) Oral Solution (Partial Waiver/Deferral/Plan) with Agreed iPSP	DGIEP	Maureen Dewey	(1)Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and (2) anorexia associated with weight loss in patients with AIDS.
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NON RESPONSIVE

NON RESPONSIVE

Syndros (dronabinol) Oral Solution (Partial Waiver/Deferral/Plan) with Agreed iPSP

- Approved Indication: (1) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and (2) anorexia associated with weight loss in patients with AIDS.
- This product triggers PREA as a new dosage form and has a PDUFA goal date of April 1, 2016
- The division clarified that the PREA requirements are based on an agreed iPSP. However, one PeRC member noted that AIDS related anorexia with weight loss is uncommon in pediatric patients and that a study in patients 15-17 years of age would likely be impossible or highly impracticable. There was considerable discussion about the prevalence of this condition based on recently published data and the division also noted that the sponsor had agreed to conduct this study. Based on the differing opinions expressed by the PeRC, the PeRC Chair asked for a vote on this PREA requirement. The PeRC voted 5-4 in favor of full waiver in pediatrics for this indication.
- *PeRC Recommendations:*
 - o The PeRC agreed with the pediatric plan for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
 - o The PeRC was split on the pediatric plan for AIDS related anorexia with weight loss (see discussion above).
 - o The PeRC reminded the division that the PREA requirement as listed in the approval letter needs to include dates for protocol submission, study completion and final study report submission.

NON RESPONSIVE

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/s/

GETTIE AUDAIN
02/18/2016



NDA 205525

INFORMATION REQUEST

Insys Therapeutics
Attention: Stephen Sherman
Vice President, Regulatory Affairs
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ 85286

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dronabinol Oral Solution.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For study INS-13-017, please submit a Define.pdf file (description of each data file and the definition of each variable) and a PD dataset for abuse potential analysis. This dataset should also include the following additional variables/data:

- Population (randomized, PD, completer, PP)
- Treatments (planned and actual)
- Sequence
- Period
- First-order Carry-over (number)
- Sex
- Emax (if applicable)
- Emin (if applicable)
- TEmax (if applicable)
- TEmin (if applicable)
- Area Under Time-Effect Curve (AUE , 0-24h)

An example of an Analysis Data Set is below:

Variable Name	Label	Type	Comments
USUBJID	Unique Subject Identifier	char	
SEQ	Sequence Number	num	
QSSEQ	Sequence	char	For example: ACBDE, or ABDCE
PERIOD	Period Number	num	
CARRY	First-order Carry-over	num	
VISIT	Visit Name	char	
VISITNUM	Visit Number	num	
TRTP	Planned Treatment	num	
TRTA	Actual Treatment	num	
TRTNAME	Name of Treatment	char	
QSTEST	Question Name	char	For example: Drug Liking, High
QSTESTN	Question Name	num	For example: 1, 2
QSCAT	Category of Question	char	VAS or ARCI
PRERESP	Pre-dose Response	num	
QSSTRESN	Numerical Results	num	
PHDCODL	PD Data: Parameter code	char	Derived parameters: Emin, Emax, TEmax, AUE(0-24), etc.
PHDCODN	PD Data: Parameter code/N	num	For example: 1, 2
QSTPT	Planned Time Point	char	For example: Pre dose, 0.5 hr
QSTPTNUM	Planned Time Point Number	num	For example: 0.5, 1.0
QSBLFL	Baseline Flag (pre-dose flag)	char	
COMPID	Completer Identifier	char	
SEX	Gender	char	

Please respond by Wednesday, November 11, 2015.

If you have any questions, contact Maureen Dewey Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., RAC
Acting Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
10/30/2015

KEVIN B BUGIN
10/30/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205525

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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) resubmission dated and received June 1, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dronabinol Oral Solution, 4.25 mg/0.85 mL.

We also refer to your correspondence, dated and received July 17, 2015, requesting review of your proposed proprietary name, Syndros.

We have completed our review of the proposed proprietary name, Syndros and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 17, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5295. For any other information regarding this application, contact Maureen Dewey, Regulatory Project Manager in the Office of New Drugs, at 301-796-0845.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
10/13/2015



NDA 205525

INFORMATION REQUEST

Insys Therapeutics
Attention: Stephen Sherman
Vice President, Regulatory Affairs
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ 85286

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dronabinol Oral Solution.

We are reviewing the pediatric section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We note that the waiver request currently included with your application is the waiver request submitted on August 12, 2014. We refer you to the agreed Pediatric Study Plan (PSP) dated May 19, 2015. The currently submitted waiver request should be replaced in Module 1.1.9 with deferral and partial waiver requests consistent with the pediatric development program outlined in the agreed PSP.

As a reminder, specifically:

A. For the indication of “(b) (4) Chemotherapy Induced Nausea And Vomiting in Patients Who Failed to Respond Adequately to Conventional Antiemetics”:

- You should request a deferral to study all ages.

B. For the indication of “Anorexia Associated with Weight Loss in AIDS”:

- You should request a deferral to study pediatric patients ages 15 to 17 years on the grounds that the product is ready for approval in adults.
- You should request a waiver to study pediatric patients ages 0 to 14 years on the grounds that studies are highly impracticable due to the small numbers.

If you have any questions, please contact Maureen Dewey Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., RAC
Acting Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
06/16/2015



NDA 205525

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Insys Therapeutics
Attention: Stephen Sherman
Vice President, Regulatory Affairs
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ 85286

Dear Mr. Sherman:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our October 10, 2014, refusal to file letter for the following:

Name of Drug Product: Dronabinol Oral Solution

Date of Application: June 1, 2015

Date of Receipt: June 1, 2015

Our Reference Number: NDA 205525

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 31, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
06/10/2015



NDA205525

REFUSAL TO FILE

Insys Therapeutics, Inc.
Attention: Steve Jensen
Senior Vice President, Regulatory Affairs
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ 85286

Dear Mr. Jensen:

Please refer to your New Drug Application (NDA) dated August 12, 2014, received August 12, 2014 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for dronabinol oral solution (5 mg/ml).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d)(3) for the following reasons:

Failure to address the requirements under the Pediatric Research Equity Act because you have provided an incomplete or inadequate pediatric study plan to conduct studies to assess the safety and effectiveness of your product for treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric patients who failed to respond adequately to conventional antiemetic treatments.

If you plan to resubmit this application, you should first submit a pediatric study plan to your IND and reach agreement with FDA per the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

Your pediatric study plan should: 1) cover the entire pediatric age range (0-17 years of age); (b) (4)



While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

1. Due to the time elapsed since the initial approval of Marinol and due to the reports of syncope that have occurred in the interim since Marinol's approval, provide a literature search and discussion on the QT prolonging potential of dronabinol. Syncope can be a manifestation of arrhythmia arising from QT prolongation.
2. Address the following Product Quality Microbiology issues:
 - a. Justify the specification for preservative content at time zero only. Traditionally, preservative content is utilized in lieu of antimicrobial effectiveness testing during stability. Submit a revised specification that includes preservative content or antimicrobial effectiveness testing at expiry.
 - b. Provide data to support the antimicrobial effectiveness of the proposed preservative system at the lower limit of the specification (i.e., (b)(4)% methyl parabens and (b)(4)% propyl parabens). Submit the test results from a minimum of one batch at or below the minimum specification for the preservative system.
 - c. Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

- i. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- ii. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method

capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Maureen Dewey, Regulatory Project Manager, at (301) 796-0845.

Sincerely yours,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
10/10/2014



IND 75228

**MEETING REQUEST-
WRITTEN RESPONSES**

Insys Therapeutics, Inc.
Attention: Willene Brondum
Senior Manager, Regulatory Affairs
444 South Ellis St.
Chandler, AZ 85224

Dear Ms. Brondum:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dronabinol oral solution.

We also refer to your submission dated August 20, 2013, containing a Type C meeting request. The purpose of the requested meeting was to discuss the abuse potential related data, and your plans for preparation of the New Drug Application submission.

Further reference is made to our Meeting Granted letter dated September 10, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 3rd, 2013 background package.

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

IND 75228

Page 2

Enclosure:

Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: IND 75228
Product Name: dronabinol oral solution
Indication: 1] Treatment of nausea and vomiting associated with cancer chemotherapy in patients who do not respond adequately to conventional antiemetics
2] Treatment of anorexia associated with weight loss in patients with AIDS

Sponsor/Applicant Name: Insys Therapeutics, Inc.
Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

Insys Therapeutics is developing an oral solution formulation of dronabinol for the treatment of nausea and vomiting associated with cancer chemotherapy and the treatment of anorexia associated with weight loss in patients with AIDS. Insys intends to submit a 505(b)(2) NDA referencing the listed drug application for Marinol (dronabinol) capsules.

FDA Advice Letter dated November 29, 2012 indicated the human abuse potential of dronabinol oral solution (Schedule I) relative to that of Marinol (Schedule III) would be required. Insys planned on submitting their 505(b)(2) NDA with in vitro analyses supportive of their proposed scheduling without human abuse potential data. FDA informed Insys on August 8, 2013, that this proposal will not provide information critical to schedule and label the product and indicated these deficiencies will impact the filability of the application.

On August 15, 2013, Insys submitted a human abuse potential study protocol INS-13-017 titled *“A Single-Dose, Double-blind, Double-dummy, Randomized, Placebo- and Active-controlled Crossover Study to Evaluate the Abuse Potential of Dronabinol Oral Solution in Recreational Cannabinoid Users.”*

On August 20, 2013, Insys submitted a type C meeting request to discuss FDA comments on the human abuse potential protocol INS-13-017, and to receive feedback on their 505(b)(2) NDA submission plans. The meeting was granted as a written response only meeting on September 10, 2013, and the background package for the meeting was received October 3rd, 2013.

2. QUESTIONS AND RESPONSES

Question 1: Please discuss the DGIEP/CSS position that the human abuse liability study is necessary for labeling and/or scheduling, and that such a study is required for filing the Dronabinol Oral Solution NDA.

FDA Response to Question 1:

Insys proposes to rely, in part, on literature and FDA's previous findings of safety and effectiveness for Marinol capsules to support the approval of its proposed Dronabinol Oral Solution. There are, however, notable differences between the two drug products, for example, differences in concentration, dosage form, and composition, that suggest that Insys's proposed Dronabinol Oral Solution product may have different abuse potential from Marinol. The proposed Dronabinol Oral Solution formulation contains 150 mg of dronabinol in 30 ml, for a concentration of 5 mg/ml, of a sweetened alcoholic solution ((b)(4)% w/w). These characteristics of the proposed Dronabinol Oral Solution may increase the likelihood of abuse and unintentional overdose, compared to Marinol, which is formulated as soft-shell capsules containing 2.5, 5 or 10 mg of dronabinol in sesame oil. The sweet taste of Dronabinol Oral Solution may also be appealing to children in accidental overdose and to individuals who may intentionally abuse the product.

Additionally, the half-life of the Dronabinol Oral Solution is twice as long as that of Marinol. This pharmacokinetic characteristic can alter the product's pharmacodynamic properties, including behavioral and subjective effects such as euphoria, drug liking and "feeling high," which may increase the abuse potential of Dronabinol Oral Solution relative to Marinol. It is also unknown how the presence of alcohol contributes to the abuse liability and other safety risks associated with the abuse of dronabinol.

As we informed you on November 29, 2012, a human abuse liability study is important information to evaluate the abuse potential (an important aspect of safety) of Dronabinol Oral Solution relative to that of Marinol capsules. It appears that you are proposing to delay the conduct of and submission of the study results of the human abuse potential study until after the application for your proposed Dronabinol Oral Solution product has been submitted. Your proposal does not otherwise address the abuse potential of your proposed product, and therefore, it lacks safety information required under the Federal Food, Drug, and Cosmetic Act (the Act) and implementing regulations, including section 505(b)(1)(A) of the Act and 21 CFR 314.50(d)(5). The Agency reviews an application for completeness at the time the application is submitted. Accordingly, the absence of the human abuse potential study or other information to address the abuse potential (an important aspect of safety) of your proposed product when the application is submitted will render the application incomplete on its face, and therefore, subject to the refusal to file regulation under 21 CFR 314.101(d)(3).¹

¹ See FDA's New Drug Evaluation Guidance Document: Refusal To File (July 12, 1993), which states that "[t]he practice of submitting an incomplete or inadequate application and then 'repairing' it in the course of an extended review period is inherently inefficient and wasteful of agency resources."

Question 2: Insys is currently awaiting comment from the CSS regarding Protocol INS-13-017 for performance of the clinical human abuse potential study previously submitted to IND 75,228 in August 2013. Does the Division or CSS have any feedback regarding Protocol INS-13-017 at this time? Please advise when final comments on Protocol INS-13-017 shall be available.

FDA Response to Question 2:

We have the following comments and recommendations to your amendments dated August 12, 2013 and August 21, 2013, containing study protocol INS-13-017 titled “*A Single-Dose, Double-Blind, Double-Dummy, Randomized, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Dronabinol Oral Solution in Recreational Cannabinoid Users.*”

1. The purpose of the study is to evaluate the abuse potential of Dronabinol Oral Solution in comparison to Marinol, a marketed Schedule III substance. Thus, the doses of your product that are tested should be equivalent in actual milligram (mg) amounts to the doses of Marinol that will be used as the positive control. The protocol should be revised so that the doses of Dronabinol Oral Solution are 10 and 30 mg, since the doses of Marinol that will be tested are 10 and 30 mg.
2. The use of a large number of abuse-related Visual Analog Scales will appropriately and adequately evaluate subjective responses that result from the administration of the test drugs. Thus, we do not see any additional value of utilizing Addiction Research Center Inventory scales in evaluating the subjective responses to the test drugs and do not recommend using these scales.

Additional comments:

Your background package also does not provide information about the container closure and dosing method. There is also no information regarding the mechanism for accurately measuring each dose (e.g., whether there is a timed lock-out system to prevent additional dosing). Given that the Dronabinol Oral Solution contains a very large amount of dronabinol, has a longer half-life than Marinol, and is formulated as a sweetened alcoholic solution, we anticipate your product may be appealing to children and to individuals who may intentionally abuse the product. As such, whether a Risk Evaluation and Mitigation Strategy (REMS) will be required may be a review issue.

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/s/

MARY H CHUNG
12/17/2013



IND 075228

MEETING MINUTES

Insys Therapeutics, Inc.
Attention: Willene M. Brondum
Senior Manager, Regulatory Affairs
10220 S. 51st Street, Suite 2
Phoenix, AZ 85044

Dear Ms. Brondum:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Dronabinol Oral Solution.

We also refer to the meeting between representatives of your firm and the FDA on April 17, 2012. The purpose of the meeting was to discuss results of your comparative bioavailability study INS-10-012 and your plans for submission of a 505(b)(2) NDA.

A copy of the official minutes of the meeting is enclosed 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) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: April 17, 2012; 9:00AM–10:00AM EST
Meeting Location: FDA – White Oak Campus
10903 New Hampshire Avenue, Building #22
Silver Spring, MD 20993

Application Number: IND 075228
Product Name: Dronabinol Oral Solution
Indication: 1) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments
2) Treatment of anorexia associated with weight loss in patients with AIDS

Sponsor/Applicant Name: Insys Therapeutics, Inc.

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)

Andrew Mulberg, M.D.	Deputy Director
Ruyi He, M.D.	Medical Team Leader
Karyn Berry, M.D.	Medical Reviewer
David Joseph, Ph.D.	Pharmacology Team Leader
Fang Cai, Ph.D.	Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Division of Metabolism and Endocrinology Products (DMEP)

Dragos Roman, M.D.	Medical Team Leader
Karen Mahoney, M.D.	Medical Reviewer

Office of Clinical Pharmacology / Division of Clinical Pharmacology III

Sue Chih Lee, Ph.D.	Team Leader
Insook Kim, Ph.D.	Reviewer

Office of Surveillance and Epidemiology / Division of Medication Error Prevention Analysis

Anne Crandall Tobenkin, Pharm.D. Safety Evaluator

Nitin Patel, Pharm.D. Safety Regulatory Project Manager

Controlled Substances Staff

Michael Klein, Ph.D.

Director

Jovita Randall-Thompson, Ph.D.

Pharmacologist

SPONSOR ATTENDEES

Insys Therapeutics, Inc.

John Kapoor, Ph.D.

Chairman of the Board

Michael L. Babich

President and Chief Executive Officer

Larry Dillaha, M.D.

Chief Medical Officer

Neha Parikh

Senior Director, Clinical Operations

Willy Brondum

Senior Manager, Regulatory Affairs

Venkat Goskonda, Ph.D.

Senior Director, Pharmaceutical

Ashok Chavan, Ph.D.

Director, Pharmaceutical Operations

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Chief Medical Officer

1.0 BACKGROUND

Insys Therapeutics is developing an oral solution formulation of dronabinol for the treatment of nausea and vomiting associated with cancer chemotherapy and the treatment of anorexia associated with weight loss in patients with AIDS. Insys intends to submit a 505(b)(2) NDA referencing the listed drug application for Marinol (dronabinol) capsules.

The sponsor submitted a type B, pre-NDA meeting request, dated February 14, 2012, to discuss results of their comparative bioavailability study INS-10-012 and plans for submission of a 505(b)(2) NDA. FDA granted Insys' meeting request in the letter dated March 7, 2012. Insys' background package was received on March 20, 2012. FDA preliminary responses were sent to the sponsor on April 13, 2012. On April 17, 2012, Insys provided additional slides in response to FDA's preliminary responses and to facilitate discussion at the meeting.

Insys' background package included results from their completed comparative bioavailability study INS-10-012. This study was a 2-treatment, 2-sequence, 4-period replicate study design to assess the bioequivalence of dronabinol oral solution 5 mg to Marinol capsules 5 mg in healthy volunteers under fasted conditions. 88 subjects were enrolled in the study. Subjects received 5 mg doses of each product on 4 occasions after a 10-hour overnight fast. Blood samples were collected for 48 hours after dosing and the plasma was analyzed for the parent compound and active metabolite. The study demonstrated bioequivalence on all PK parameters except AUC. Dronabinol oral solution had approximately 35% higher AUC than the reference Marinol

capsule. Insys claims that this increase in AUC is negligible taking into consideration the animal-to-human safety margin and the demonstrated bioequivalence for C_{max} , AUC over the recommended range of dosing intervals for the parent compound, and for all parameters regarding the active metabolite. The sponsor notes that results of a literature search conducted to identify adverse events associated with the use of oral dronabinol further supports the safety of the proposed product. Insys indicated that there were no appreciable differences with respect to adverse events observed between dronabinol oral solution and Marinol capsules from their comparative bioavailability study.

2.0 DISCUSSION

The format of these minutes provides for Insys Therapeutic's questions in regular typeface, followed by the Agency's April 13, 2012 responses in **bolded** print. The April 17, 2012 meeting discussion is presented in *italic and bolded* print.

Meeting Discussion:

Insys explained that the proposed dronabinol oral solution is an attempt to optimize the formulation to allow greater flexibility to titrate the administered dose. Insys has focused on developing supportive care products for cancer patients. The sponsor has previously obtained approval for a fentanyl spray for breakthrough cancer pain. They have also received approval for a generic dronabinol capsule.

Insys had no further comments on FDA's responses to questions #1 and 2. Insys will submit their comments on FDA's responses to questions #3 and 4 in writing to the IND.

2.1 FDA INTRODUCTORY COMMENTS:

1. According to your background information, bioequivalence was not demonstrated between your product, Dronabinol Oral Solution and the listed reference product (Marinol). We note that your product resulted in a 35% higher AUC_{inf} (90% CI: 125.86; 143.76).
2. Because the AUC of your product is higher than that of the listed reference product (Marinol), you will need to provide adequate safety data that supports the use of your product at the highest dose for each proposed population.

Meeting Discussion:

Insys stated that the safety of dronabinol is well characterized and established by historical information. The sponsor also believes that the 35% increase in AUC for dronabinol oral solution is negligible as bioequivalence was met on the other PK parameters. Insys noted that the metabolite, which is substantially active, demonstrated bioequivalence. FDA replied that bioequivalence needs to be met on all PK parameters for a product to be considered bioequivalent.

Insys must provide adequate safety data for each population of intended use. FDA noted that populations have changed since the initial Marinol approval. Furthermore, polypharmacy concerns must be addressed. If Insys proposes to lower the maximum dose, then exploration of a narrower therapeutic index must be addressed.

Refer to the sponsor's slides 3 and 4. With reference to the sponsor's comparative bioavailability study, Insys indicated that the number of adverse events observed between the dronabinol oral solution and Marinol were similar. However, the duration of adverse events was considerably shorter in subjects administered dronabinol oral solution.

Insys proposed a literature based approach as part of the safety database and to support use in each population. FDA did not agree. FDA re-iterated that a clinical study(ies) must be conducted in the population(s) of interest to provide adequate safety for the product. Details of the proposed clinical safety study will need to be discussed further.

FDA noted that Insys may request a meeting with DMEP to discuss specific issues regarding the indication for treatment of anorexia associated with weight loss in patients with AIDS.

- 3. Independently of whether Dronabinol Oral Solution is filed under a 505(b)(2) NDA with Marinol, a Schedule III drug, as the reference drug, you must characterize the abuse potential of the formulation. The proposed oral solution does not have the same abuse potential as Marinol (Schedule III) capsules formulated in sesame oil. Scheduling of the oral solution will be based upon the evaluation of all data related to the abuse potential of this formulation. You should not assume that the DEA will place your product in the same schedule as that of Marinol.**
- 4. Relative to Marinol:**
 - a. Your assessment of abuse potential of the product should address the ease with which your product can be abused by alternate routes of administration.**
 - b. For example, the assessment of abuse potential should address possible abuse by alternate routes, including smoking and intravenous injection.**
 - c. Marinol and other cannabinoids should be used as positive controls in assessing the abuse potential of the product.**
- 5. You should develop a plan designed to evaluate and address the abuse potential evaluation of your drug product.**
 - a. Protocols should include detailed outlines of *in vitro* (physicochemical) and *in vivo* procedures used to evaluate the ease with which the API can be extracted for abuse by alternate routes.**
 - b. The methodology used in all your studies should be justified.**

- c. A clinical abuse liability study may need to be conducted.
- d. All studies should be conducted on the to-be-marketed formulation.
- e. CSS is available to comment on your proposed plan prior to the commencement of your studies.

Meeting Discussion:

FDA clarified that the difference in formulation of the dronabinol oral solution may lend itself to potential more abuse than the reference Marinol product. Marinol capsules are formulated in sesame oil. Dronabinol oral solution is formulated in 50% ethanol and approximately 30% water, and may be more easily abused because of the formulation. FDA stated that Marinol is a Schedule III substance, but dronabinol oral solution is a Schedule I substance under the Controlled Substances Act.

The sponsor should submit a proposal to address this difference and justify that the abuse potential of their dronabinol oral solution formulation is equal to or less than Marinol.

2.2 CLINICAL QUESTIONS

Question 1: Because data on Dronabinol Oral Solution is derived from one bioequivalence study (INS-10-012), Insys does not plan to include an Integrated Summary of Efficacy (ISE) in Module 5 of the NDA. In lieu of the development of an ISE, Insys will provide a short explanation and refer to the Summary of Clinical Efficacy in Module 2, as well as the final study report in Module 5. Does the Agency agree with this approach?

FDA Response:

Your approach is acceptable.

2.3 NONCLINICAL QUESTIONS

Question 2: 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 Marinol[®]. Insys will supplement this review with any new nonclinical literature on dronabinol published since the approval of Marinol (May 31, 1985). Does the Agency concur with this approach?

FDA Response:

Your question suggests that you are proposing to reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries for support of safety and/or efficacy. A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug, may rely only on that finding as is reflected in the approved labeling for the listed drug. The nonclinical information in the Marinol labeling is appropriate and may be sufficient to satisfy the nonclinical requirements for your proposed NDA submission, based on the information in your briefing package. You may also rely

upon published nonclinical literature on dronabinol but the utility of any submitted publication as supportive information for your NDA will be determined based on the Agency's review and evaluation.

2.4 CHEMISTRY, MANUFACTURING, AND CONTROLS QUESTIONS

Question 3: Insys proposes submission of stability data as per full ICH guidelines the NDA for one lot with 36 months long-term data and two additional lots with three months long-term and accelerated data. Insys plans to provide stability data updates for the second and third registration lots throughout the NDA review and commits to provide no updates beyond 3 months prior to the PDUFA date. Is this approach acceptable?

FDA Response:

Due to review timelines that are dictated by our Good Review Management Practices (GRMP) policy, we will not be able to accept stability data beyond the mid-cycle of the review clock. Any data received after the 5th month of the review clock will not be considered in establishing the expiration dating period for your product.

Question 4: The proposed container closure system for Dronabinol Oral Solution is a 30 mL amber glass (b) (4) equipped with a child-resistant closure with tamper resistant wrapping packaged in a suitably sized carton with a 1 mL syringe for dosing.

- a. Does the Agency have any additional requirements Insys should consider for packaging of the subject drug product?

FDA Response:

The proposed container closure system appears appropriate for the drug product, given that it is a controlled substance, and the bottle size is appropriate for a month supply of the recommended dose. However, we would like to review a mock up of the bottle which includes the affixed label to provide a more comprehensive evaluation of the proposed product.

Please clarify if the drug product has to be stored in a glass container or if it can be transferred or divided into smaller plastic containers or syringes. Additionally, is the proposed formulation light sensitive requiring storage in an amber bottle?

- b. Is Insys' proposal to package a 1 mL syringe with Dronabinol Oral Solution to ensure accurate dosing acceptable to the Agency?

FDA Response:

If you choose to co-package a 1 mL syringe with Dronabinol Oral Solution, your application will be considered a combination product [see 21 CFR 3.2(e)] and will require review from the Center for Devices and Radiological Health (CDRH). You will need to

provide details on the syringe component including information on the syringe supplier, a description of the manufacturing process and materials used to produce the syringe, and how the syringe will be used with the oral solution product.

(b) (4)

Meeting Discussion:

Insys will incorporate the changes recommended by FDA. Per discussions with the syringe supplier, Insys noted concern with (b) (4) due to the size of the syringe.

2.5 ADDITIONAL FDA COMMENTS:

- 1. We recommend that you characterize multiple-dose PK for Dronabinol Oral Solution for the labeling. We recommend that you characterize PK at the highest dose with most frequent dosing.**

Meeting Discussion:

Refer to the sponsor's slide 1. Insys noted that the highest approved dose and frequency of administration in the approved label for Marinol is not consistent with current medical practice. Insys explained that when the reference Marinol product was initially approved, patients usually received HEC or MEC in the inpatient setting. High dronabinol doses from 7 mg/m² up to 15 mg/m² every 4-6 hours were administered. With the approval of the 5-HT₃ and NK₁ antagonists, administration of chemotherapy was transitioned to the outpatient setting. There is still a challenge in addressing anticipatory, delayed, breakthrough, and refractory nausea and vomiting. Marinol is useful but the dose administered is less than that originally approved in order to minimize adverse effects and allow patients to maintain functionality. In

practice today, the starting Marinol dose is 2.5 mg t.i.d. and increased up to 5 mg t.i.d. if necessary.

Refer to the sponsor's slide 2. Insys proposed a multiple-dose PK study (b) (4)

FDA noted that the sponsor intends to file a 505(b)(2) NDA relying on the Agency's previous findings of safety and efficacy for the listed reference drug, Marinol. (b) (4)

(b) (4)

FDA explained that the multiple-dose PK study was requested to obtain PK data specific to dronabinol oral solution for labeling as the proposed product is not bioequivalent to the listed reference drug. Furthermore, evaluation of the highest dose was requested to address the potential safety concern with dronabinol oral solution due to the higher AUC.

(b) (4)

FDA suggested conducting the PK study in patients rather than healthy volunteers. For the multi-dose PK study, Insys needs to characterize the highest dose that will be included in labeling.

(b) (4)

FDA indicated that such a change in labeling would need to be supported by the appropriate clinical data. (b) (4)

Alternatively, Insys needs to conduct a clinical safety study(ies) in the intended population(s) of use.

Insys asked if it would be acceptable to (b) (4)
conduct a new study to demonstrated bioequivalence. FDA agreed that such a proposal may be adequate.

2. Based on the submitted data, the proposed Dronabinol Oral Solution does not meet the bioequivalence criteria when compared to the currently marketed dronabinol capsules. As a result, the proposed Dronabinol Oral Solution may have different dose recommendations compared to the capsules. Errors could occur between the two dronabinol products because health care providers may assume the two are bioequivalent, and therefore interchangeable during prescribing and dispensing which can result in underdose or overdose.

Meeting Discussion:

FDA stated that the concern of potential dosing errors may be addressed through labeling.

3. As noted in FDA's end of phase 2 meeting minutes dated September 20, 2010 and preliminary comments correspondence dated August 14, 2009, we remind you that many of the proposed impurity limits are generally higher than the actual levels observed in your stability batches.
4. The Pediatric Research Equity Act (PREA) of 2007 requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived, deferred, or exempt (i.e., orphan designation letter issued). Therefore, in order to fulfill the PREA requirements, you should formulate a pediatric clinical development plan that incorporates all pediatric age ranges (0 to 16 years). Include in the plan any planned or ongoing pediatric studies, the specific age groups that will be studied, and any age groups to be deferred or waived. If you are planning to request a waiver for certain indications or age groups, you should provide an adequate justification. If you submit a deferral for pediatric studies, certification of the grounds for deferring any assessments should be included. You should also provide a timeline for completion of any planned pediatric trials to include the following milestone dates: final protocol submission, study completion, and final study report.
5. **Prescribing Information**
Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

6. Manufacturing Facilities

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

7. 505(b)(2) Regulatory Pathway

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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf> . 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://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.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.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

3.0 ACTION ITEMS

1. FDA agreed to review and have further discussions with Insys regarding the details of their proposed clinical safety study(ies) to be conducted in the intended population(s) of use. Polypharmacy concerns must also be addressed.
2. For the multi-dose PK study, Insys must characterize the highest dose that will be included in the product labeling.
3. FDA agreed that Insys may (b) (4) conduct a new study to demonstrate the bioequivalence of their proposed product to the listed reference drug.
4. Insys should submit for FDA review their proposal to assess the abuse potential of dronabinol oral solution.

4.0 ATTACHMENTS AND HANDOUTS

1. Insys slides dated April 17, 2012

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JAGJIT S GREWAL
05/22/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075228

MEETING MINUTES

Insys Therapeutics, Inc.
Attention: Willene M. Brondum
Senior Manager, Regulatory Affairs
10220 S. 51st Street, Suite 2
Phoenix, AZ 85044

Dear Ms. Brondum:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dronabinol oral solution.

We also refer to the meeting between representatives of your firm and the FDA on May 13, 2010. The purpose of the meeting was to discuss your responses to the FDA comments dated August 14, 2009, your clinical development program, and to obtain concurrence for submission of a 505(b)(2) NDA.

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) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 13, 2010; 2:00PM – 3:00PM EST
Meeting Location: FDA – White Oak Campus
10903 New Hampshire Avenue, Building #22
Silver Spring, MD 20993

Application Number: IND 075228
Product Name: Dronabinol Oral Solution
Indication: Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments.

Sponsor/Applicant Name: Insys Therapeutics, Inc.

Meeting Chair: Nancy Snow, D.O., M.P.A.
Meeting Recorder: Jagjit Grewal, M.P.H.

FDA ATTENDEES

Division of Gastroenterology Products

Donna Griebel, M.D.	Director
Nancy Snow, D.O., M.P.A.	Acting Medical Team Leader
Tamara Johnson, M.D.	Medical Reviewer
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Office of Clinical Pharmacology

Jane Bai, Ph.D.	Reviewer
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Office of New Drug Quality Assessment

Marie Kowblansky, Ph.D.	Pharmaceutical Assessment Lead
-------------------------	--------------------------------

Controlled Substances Staff

Jovita Randall-Thompson, Ph.D.	Pharmacologist
--------------------------------	----------------

SPONSOR ATTENDEES

Insys Therapeutics, Inc.

John Kapoor, Ph.D.	CEO
Mr. Mike Babich	President & COO
Larry Dillaha, M.D.	CMO
Venkat Goskonda, Ph.D.	Sr. Director, Pharm. Development & Regulatory Affairs
Ashok Chavan, Ph.D.	Director, Quality Control & Quality Assurance
(b) (4)	Clinical Pharmacology & Biopharmaceutics Consultant
(b) (4)	Biostatistics Consultant

1.0 BACKGROUND

Reference is made to Insys Therapeutics' request for an end of phase 2 meeting dated June 16, 2009. An industry meeting was scheduled for August 18, 2009, but was cancelled per request of the sponsor on August 17, 2009. Insys noted that additional time was needed to address the concerns outlined in the FDA preliminary responses dated August 14, 2009.

Insys Therapeutics submitted a type B, end of phase 2 meeting request, dated January 11, 2010, to discuss their clinical development plan and the FDA preliminary response correspondence dated August 14, 2009. FDA granted Insys' meeting request in the letter dated January 28, 2010. The industry meeting was initially scheduled for April 7, 2010, but was later rescheduled for May 13, 2010. FDA requested that the meeting be rescheduled to allow additional time to evaluate the sponsor's proposed clinical development program. Insys Therapeutics' background package was received on March 10, 2010. FDA preliminary responses were sent to the sponsor on May 7, 2010.

As outlined in their meeting background package, the sponsor is developing dronabinol oral solution for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments. Insys intends to submit a 505(b)(2) NDA referencing Marinol (dronabinol) capsules. Insys has completed the following PK studies.

Study	Type of Study
	(b) (4)
INS-06-006	Ascending dose study in healthy volunteers using a syrup formulation for the oral administration of dronabinol (2.5mg, 5mg, 10mg).
	(b) (4)

Insys claims that the dronabinol oral solution product will have at least as favorable safety profile as the referenced Marinol product. Additionally, the oral solution formulation exhibits reduced inter subject variability as compared to Marinol capsules and achieves estimated threshold plasma concentration for its antiemetic activity faster than observed with Marinol.

Insys proposed a scaled bioequivalence approach to take into account the high variability of the reference product (Marinol capsule). The sponsor proposed 2 studies which will allow for both

the determination of whether the reference drug is highly variable and the analysis of average bioequivalence.

Study	Type of Study
(b) (4)	
INS-10-012	A fasting two-treatment, two-period, crossover study comparing Insys' Dronabinol Oral Solution to Marinol capsule 5mg in a number of subjects sufficient to meet study statistical power requirements and then apply adjusted BE criteria.

Regarding their chemistry and manufacturing development, Insys will provide scientific justification for the proposed specification limit, detailed information on the manufacturing plan, and will place 2 additional lots manufactured at no less than pilot scale on stability (data will be submitted with NDA).

Additionally, Insys has obtained Schedule I registration from DEA to conduct research activities with dronabinol oral solution. Insys will submit a proposal for scheduling dronabinol oral solution.

2.0 DISCUSSION

The format of these minutes provides for Insys Therapeutics' questions in regular typeface, followed by the Agency's May 7, 2010 responses in **bolded** print. The May 13, 2010 meeting discussion is presented in *italic and bolded* print.

2.1 QUESTIONS

1. Is the strategy and the two studies outlined above (*FDA note: see sponsor background package dated 3/9/10*) and described in more detail in Attachment 4 an acceptable approach to establish bioequivalence between its Dronabinol Oral Solution and Marinol capsules?

FDA Response:

We acknowledge your proposal to use "adjusted/scaled bioequivalence criteria approach" based on a presentation presented by OGD at an AAPS meeting. However, as ANDAs and OGD operate under a different regulatory framework, OCP is not bound by their decisions as, on the New Drugs side of the Agency, OCP is permitted to evaluate not just the confidence interval but also the clinical response, disease state factors, etc. in reaching conclusions regarding bioequivalency. Our recommendation regarding establishing bioequivalence for your drug is that you refer to the approaches outlined in the "Guidance for Industry: Statistical Approaches to Establishing Bioequivalence" (January 2001). An adjusted or scaled approach could be used, but it

would only be evaluated as additional information, with the primary determination of bioequivalence made on the standard two 1-sided test (log transformed 90% confidence intervals) in conjunction with the clinical performance of your drug as referred to above. A replicated study design may be used. We recommend that you calculate the number of subjects needed for the bioequivalence study based on your chosen study design and intra-subject variability. The latter may be estimated from the results of your proposed PK study, entitled "A Study of Intra-Subject Variability of the Bioavailability of Marinol Capsules 5 mg under Fasted Conditions." If your PK comparability study fails to demonstrate bioequivalence between your product and the listed product, then you need to conduct clinical studies. Efficacy studies are needed if your product has lower systemic exposure than the listed product and safety studies are needed if your product has higher systemic exposure than the listed product. Though you do not need to establish bioequivalence for both parent and its metabolite, which is active as well, we strongly recommend that you determine the PK for both parent and its active metabolite, 11-hydroxy-delta-9-tetrahydrocannabinol.

Meeting Discussion:

Insys agreed with the FDA responses to questions #3, #4, and the FDA additional comments.

Insys explained that they are attempting to optimize the formulation for dronabinol to work better clinically. Insys noted that the dronabinol is a highly variable drug. Insys further noted that a traditional bioequivalence study would require 600 to 800 patients. FDA explained that the Office of Clinical Pharmacology has not adopted the proposed scaled bioequivalence approach. Furthermore, the Office of Generic Drug's (OGD) scaled bioequivalence approach has been revised. FDA recommended that the sponsor refer to the cited guidance and conduct a traditional bioequivalence analysis. For highly variable drugs, a replicated study design would be recommended as outlined in the guidance.

Insys asked for additional clarification of why the scaled bioequivalence approach was not acceptable. FDA replied that for a 505(b)(2) application, bioequivalence is only 1 parameter that is evaluated. Pharmacokinetics (PK) as well as pharmacodynamics (PD), disease situation, characteristics of the population and other factors are considered. FDA believes that traditional bioequivalence is the best approach for the proposed product.

Insys noted that a large number of study subjects would be needed to demonstrate strict bioequivalence due to the high variability of dronabinol. Insys asked if they could conduct the scaled bioequivalence approach and submit the results as a review issue. Insys would also conduct an analysis with an average bioequivalence method. FDA replied that submission of only a scaled approach analysis would not be accepted for review. FDA has not seen the statistical analysis to justify the study sample size. FDA noted that the sponsor can use their intra-subject PK variability study to plan for a traditional bioequivalence study. FDA will provide comment on the sponsor's PK variability study and sample size justification.

Insys asked if another meeting could be held to discuss other possible data, such as utilization of PD endpoints, to support efficacy and safety if they are unable to demonstrate strict bioequivalence. FDA stated that the sponsor may submit their protocol for review of proposed PD endpoints or biomarkers to establish bioequivalence. FDA would review the information to determine if this could be an alternative route to pursue. Based upon the proposed indication, it would be difficult to determine an appropriate PD endpoint other than a clinical endpoint. FDA asked if the sponsor had an idea of the sample size for an efficacy study. Insys had not yet determined a sample size, but commented that the trial would be placebo-controlled.

FDA asked what type of chemotherapy, highly emetogenic (HEC) or moderately emetogenic (MEC), would be used in the trial. Insys commented that at least MEC would be included. The sponsor still needs to discuss the details of such a trial. FDA noted that a protocol would need to be reviewed for any additional comments. The sponsor should consider the type of emetogenicity, what patients are targeted, and what the product would be used for (prevention versus rescue medication) in addition to other factors in designing the trial.

Insys stated that there is available data regarding second line therapy for CINV. Insys noted that the proposed dronabinol oral solution has a faster onset of action than the reference drug. Per their comparative PK study, 15 out of 18 patients achieved significant blood levels after 15 minutes with dronabinol oral solution versus 1 hour with Marinol. The sponsor expects a 50% or more reduction in variability. FDA recommended that the sponsor refer to PPI drugs, such as lansoprazole, which have high variability and use these as examples in development of their PK and bioequivalence studies.

Insys stated that their formulation was developed with clinical endpoints in mind. The proposed dronabinol oral solution was designed to reduce variability as seen with Marinol, which also translates to a clinical response and a shift in the PK curve for faster onset. The sponsor planned for at least an equivalent AUC and an acceptable C_{max} not to raise safety concerns. FDA replied that the T_{max} is less than half an hour shorter than the reference product. Additionally, the dronabinol oral solution has a lower C_{max} and the AUC for the active metabolite is also lower. Both the parent compound and the active metabolite have an effect. Insys replied that if activity is per the parent compound and the active metabolite, then both are needed in the bloodstream. When the two are combined, the effect is equivalent to Marinol, but the profile is slightly different.

Insys commented that the lower C_{max} for the dronabinol oral solution may provide some safety benefit. FDA stated that per the guidance, a PK comparability study would provide an evaluation of C_{max} and AUC. A clinical endpoint is most likely needed, since there is no readily available PD endpoint. The sponsor should make an effort to meet the bioequivalence criteria. Insys asked if the dronabinol oral

solution product would be considered safe and effective if it had a lower C_{max} and a similar AUC to Marinol. FDA indicated that there was not enough information available to determine which PK parameter, C_{max} or AUC, correlates with efficacy.

2. If the proposed strategy is acceptable, will one study, establishing bioequivalence between Insys' Dronabinol Oral Solution and Marinol capsules support (i) an NDA filing under Section 505(b)(2) for Dronabinol Oral Solution, and (ii) an indication for Dronabinol Oral Solution that matches the Marinol capsule labeling (i.e., "...treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.")?

FDA Response:

See the response to Question #1. In addition to a PK comparability study, you need to conduct a food effect study for your proposed product.

Meeting Discussion:

Insys asked if a food effect study was needed. Insys noted that for [REDACTED] (b) (4). FDA replied that the sponsor should provide a rationale as to why a food effect study is not needed. The Marinol product label does not contain information on food effects.

Insys explained that it is rare to take dronabinol with food. Insys asked how conducting such a study would provide useful information if the product is not used in this manner. FDA stated that dronabinol is an old drug and a food effect study may provide useful information resulting in better options for patients. FDA indicated that the food effect study was recommended, but not a requirement. FDA also commented that for generic drugs, bioequivalence must be established in fasted and fed states.

3. For a 505(b)(2) application, based on the FDA's previous finding of the safety and efficacy of Marinol capsules, would there be any other requirements [e.g., as related to clinical pharmacology/bioavailability aspects in the context of meeting 21CFR Part 320 (Bioavailability and Bioequivalence Requirements), etc.]?

FDA Response:

See the responses to Questions #1 and #2. A bioequivalence study is acceptable for an NDA filing under section 505(b)(2) submission provided that the formulation used in the PK comparability study is the same as the to-be-marketed formulation.

Meeting Discussion:

No discussion occurred.

4. In addition to a discussion and resolution regarding the acceptability of the above-proposed strategic approach and study design, Insys wishes to obtain FDA concurrence with the proposed approaches to address FDA concerns regarding Chemistry, Manufacturing, and Controls as described in Attachment 1.

FDA Response:

The individual and total impurity limits proposed in your briefing package (Table 13 of Attachment 2) are generally higher than the actual levels of impurities found in your stability batches (even after 12 months of storage). The acceptability of these limits will be further evaluated when you submit additional data (additional batches and additional stability time points).

Meeting Discussion:

No discussion occurred.

Additional FDA Comments:

1. We remind you of the Pediatric Research Equity Act (PREA) of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived, deferred, or exempt (i.e., orphan designation letter issued). Therefore, in order to fulfill the PREA requirements, you should formulate a pediatric clinical development plan that incorporates all pediatric age ranges. You should also provide a timeline for completion of the planned pediatric trials. If you are planning to request a waiver for certain indications or age groups, you should provide a justification.
2. 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/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.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

1. Insys' proposed scaled bioequivalence method is not acceptable. Insys should refer to the cited guidance in the response to Question #1 and conduct a traditional bioequivalence study. Insys should submit the study protocol and sample size justification for FDA review.
2. A food effect study is recommended, but not required.

5.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

JAGJIT S GREWAL
09/20/2010