CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205525Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **July 1, 2016**

From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 205525**

Subject: Final Recommendation for NDA 205525

At the time when the CMC Review #1 was completed on February 29, 2016, it had noted the following pending issues:

- The label/labeling issues were not resolved.
- The CDRH consult reviews for the press-in bottle adapter and oral syringe were not completed from the Office of Compliance and Office of Device Evaluation.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

In accordance with CDER Product Title Guidance and USP monographs, the drug product title is as follows: SYNDROS (dronabinol) oral solution. The immediate container label and carton labels were revised accordingly and resubmitted on June 23, 2016. The package insert was revised and resubmitted on June 30, 2016. The CMC sections of the package insert, immediate container label and carton label were reviewed by Dr. Hitesh Shroff and found acceptable (**Attachment – 1).**

On June 3, 2016, the Office of Process and Facilities issued the overall "Approval" recommendation for the facilities involved in this NDA (**Attachment – 2)**.

The Office of Device Evaluation, CDRH, concluded that there is little likelihood of adverse systemic, genotoxic or carcinogenic effects after patients are exposed to the compounds extracted from the press-in bottle adapter and oral syringe. (see the Biocompatibility of the Device Constituents Review conducted by Dr. Kathleen Fitzgerald dated March 21, 2016).

The Office of Compliance, CDRH, has issued a final approval recommendation for the applicant's Quality System Requirements for the drug product based on the review conducted by Dr. Bleta Vuniqi dated June 6, 2016.

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from the OPQ perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
DNDP II/ONDP/OPQ
July 1, 2016

Hitesh N. Shroff -A

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Attachment 1:

1. *Package Insert*

(a) "Highlights" Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYNDROS safely and effectively. See full prescribing information for SYNDROS.

SYNDROS (dronabinol) oral solution, CX
Initial U.S. Approval: 1985

——————DOSAGE FORMS AND STRENGTHS ——————
Oral Solution: 5 mg/ mL (3)

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

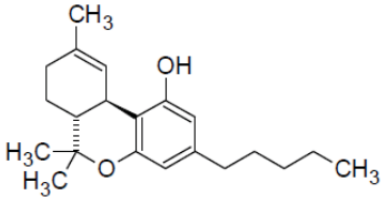
3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 5 mg/mL, a clear, pale yellow to brown solution.

#11. Description

11 DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. Dronabinol has the following empirical and structural formulas:



$C_{21}H_{30}O_2$ (molecular weight=314.46)

Dronabinol is a clear colorless to amber oil. Dronabinol is insoluble in water. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

SYNDROS (dronabinol) oral solution, 5 mg/mL is a clear, pale yellow to brown solution. Each mL of SYNDROS contains 5 mg of dronabinol as an active ingredient and the following inactive ingredients: 50 % (w/w) dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole, and water.

#16 How Supplied/storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

- SYNDROS (dronabinol) oral solution, 5 mg/mL is a clear, pale yellow to brown solution. SYNDROS is supplied in a multi-dose, clear, amber-colored 30 mL glass bottle. It is closed with a 20 mm child-resistant, white polypropylene screw cap with a Teflon coated liner. The bottle is wrapped with a polyvinyl chloride body band to provide tamper evidence and packaged in a carton with an oral syringe, and a push-in bottle adapter.

  NDC 20482-335-30 (30 mL multi-dose bottle, an oral syringe and a push-in bottle adapter)

- Store in a refrigerator between 2°C and 8°C (36°F and 46°F); excursions permitted to 15°C and 25°C (59°F and 77°F). The opened bottle can be stored at 25°C (77°F). Discard unused portion 28 days after first opening [see USP Controlled Room Temperature].

- Keep SYNDROS oral solution and the oral syringe in the supplied carton.

2. ***Labels***

Immediate Container Label

(b) (4)

Container Carton Label

(b) (4)

Reviewer's Assessment and Signature:

The final immediate container and carton labels submitted on June 23, 2016 and the package insert submitted on June 30, 2016 are satisfactory from ONDP perspective.

Reviewer's Signature:
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Hitesh N. Shroff -A

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Date: 2016.07.01 08:31:24 -04'00'

Secondary Review Comments and concurrence:

Supervisor's Signature:
Moo-Jhong Rhee, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Moojhong Rhee -S

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Attachment 2:

Facilities: "Approve" recommendation was entered in Panorama on June 3, 2016.

Submission Overall Manufacturing Facility Status

Overall Status	Completion Date	Project Name
Approve	6/2/2016	NDA-205525-ORIG-1-RESUB-4
Not Applicable	5/3/2016	NDA-205525-ORIG-1-RESUB-4
Pending		NDA-205525-ORIG-1

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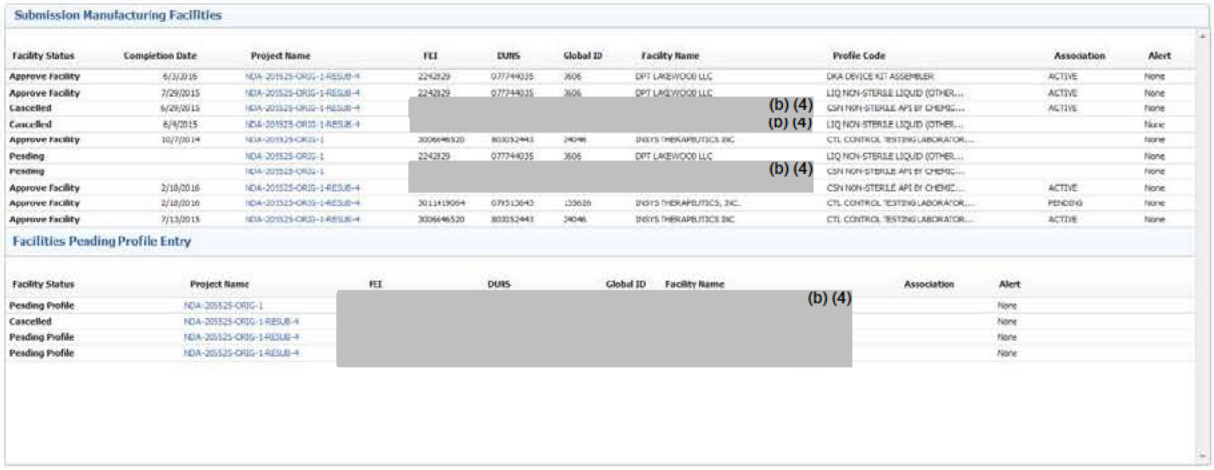

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEI	DUNS	Global ID	Facility Name	Profile Code	Association	Alert
Approve Facility	6/2/2016	NDA-205525-ORIG-1-RESUB-4	2242829	077744035	3606	DPT LAKEWOOD LLC	DKA DEVICE KIT ASSEMBLER	ACTIVE	None
Approve Facility	7/29/2015	NDA-205525-ORIG-1-RESUB-4	2242829	077744035	3606	DPT LAKEWOOD LLC	LIQ NON-STERILE LIQUID (OTHER...	ACTIVE	None
Cancelled	6/29/2015	NDA-205525-ORIG-1-RESUB-4				(b) (4)	CSN NON-STERILE API BY CHEMIC...	ACTIVE	None
Cancelled	6/4/2015	NDA-205525-ORIG-1-RESUB-4				(D) (4)	LIQ NON-STERILE LIQUID (OTHER...		None
Approve Facility	10/7/2014	NDA-205525-ORIG-1	3006646520	803052443	24046	INSYS THERAPEUTICS INC	CTL CONTROL TESTING LABORATOR...		None
Pending		NDA-205525-ORIG-1	2242829	077744035	3606	DPT LAKEWOOD LLC	LIQ NON-STERILE LIQUID (OTHER...		None
Pending		NDA-205525-ORIG-1				(b) (4)	CSN NON-STERILE API BY CHEMIC...		None
Approve Facility	2/18/2016	NDA-205525-ORIG-1-RESUB-4					CSN NON-STERILE API BY CHEMIC...	ACTIVE	None
Approve Facility	2/18/2016	NDA-205525-ORIG-1-RESUB-4	3011419064	079513643	135626	INSYS THERAPEUTICS, INC.	CTL CONTROL TESTING LABORATOR...	PENDING	None
Approve Facility	7/13/2015	NDA-205525-ORIG-1-RESUB-4	3006646520	803052443	24046	INSYS THERAPEUTICS INC	CTL CONTROL TESTING LABORATOR...	ACTIVE	None

Facilities Pending Profile Entry

Facility Status	Project Name	FEI	DUNS	Global ID	Facility Name	Association	Alert
Pending Profile	NDA-205525-ORIG-1				(b) (4)		None
Cancelled	NDA-205525-ORIG-1-RESUB-4						None
Pending Profile	NDA-205525-ORIG-1-RESUB-4						None
Pending Profile	NDA-205525-ORIG-1-RESUB-4						None

Hitesh Shroff

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Recommendation: This 505(b)(2) application is **not** deemed ready for approval as of this review in its present form, per 21 CFR 314.125(b)(6).

NDA 205525
Review 1
Review Date

Drug Name/Dosage Form	SYNDROS (dronabinol) solution
Strength	4.25mg/ 0.85ml
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Insys Development Company, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission	June 1, 2015
Amendment	02-Jul-2015
Amendment	08-Oct-2015
Amendment	11-Nov-2015
Amendment	16-Nov-2015
Amendment	30-Nov-2015
Amendment	10-Dec-2015
Amendment	22-Jan-2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffery Medwid	OMPT/CDER/OPQ/ONDP/DND API/NDBII
Drug Product	Hitesh Shroff	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Process	Kelly Forney-Stevens/Peter Krommenhoek	OMPT/CDER/OPQ/OPF/DPAIII/ PABVIII
Microbiology	Jonathan Swoboda	OMPT/CDER/OPQ/OPF/DMA/M ABIII
Facility	Vipul Dholakia	OMPT/CDER/OPQ/OPF/DIA/IA BIII
Biopharmaceutics	Peng (Vincent) Duan	OMPT/CDER/OPQ/ONDP/DB/ BBII
Project/Business Process Manager	Truong Quach	OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI
Application Technical Lead	Hitesh Shroff	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/DMP TPO/MDTP
Environmental Assessment (EA)	Hitesh Shroff	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV

Table of Contents

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS [1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	08-Feb-2016	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75228	Dronabinol oral solution
ANDA	78501	Dronabinol capsules
NDA	18651	Dronabinol capsules for nonclinical and clinical findings of safety and efficacy.

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH/ODE	Complete	Acceptable	04-Feb-2016	Dr. Kathleen Mollo
CDRH/OC	Pending			Dr. Bleta Viniqi
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

The Office of Facility and Process has made a final overall manufacturing Inspection "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the label/labeling issues have ***not*** been completely resolved as of this review and the device consult review from the Office of Compliance, CDRH is still pending.

Therefore, from the OPQ perspective this NDA is not deemed ready for approval at this time in its present from per 21 CFR 314.125(b)(6) and 21 CFR 314.125(b)(13), until the above issues are satisfactorily resolved. **(see the List of Deficiencies on p. 99)**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

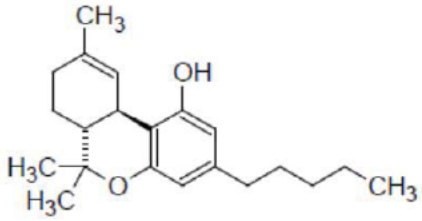
II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The active pharmaceutical ingredient in the drug product is Dronabinol, USP. It is manufactured by (b) (4). The detailed CMC information of dronabinol is provided in (b) (4) DMF (b) (4). The applicant provided an LoA to reference DMF (b) (4) for the CMC information. The DMF was reviewed on February 8, 2016 and found to be adequate.

Dronabinol, USP is a clear, colorless to amber glassy solid. It is lipophilic and practically insoluble in water. It is produced in (b) (4) as the starting materials. The bulk drug substance is stored in a (b) (4) The glass container and the adapter are stored in (b) (4). The recommended re-test period is (b) (4) when stored at (b) (4) in the container closure system described above.

Its chemical name is(6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. Dronabinol has the following molecular and structural formulas:



$C_{21}H_{30}O_2$ (molecular weight=314.46)

Dronabinol, USP manufactured and controlled according to the procedures described in [redacted] (b) (4) DMF [redacted] (b) (4) conforms to the requirements (specification) for formulation of dronabinol solution as described in this NDA.

B. Drug Product [Established Name] Quality Summary

Dronabinol solution is a cannabinoid indicated in adults for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy in patients.

Dronabinol solution, 4.25 mg/0.85 mL is a clear, pale yellow to brown solution. Each 0.85 mL of dronabinol solution contains 4.25 mg of dronabinol as an active ingredient and the following inactive ingredients: 50% dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methylparaben, propylparaben and butylated hydroxyanisole and water.

The drug product is supplied in a multi-dose, clear amber-color glass 30-mL bottle closed with a 20 mm child-resistant, white polypropylene screw cap with a Teflon coated liner. The bottle is wrapped with a polyvinyl chloride body band to provide temper evidence and packaged in a carton with an oral syringe, and a push-in bottle adapter.

The drug product manufacturing process involves [redacted] (b) (4) key steps:

[redacted] (b) (4)

The drug product manufacturing process proposed by the applicant with the following critical manufacturing parameters and in-process controls to produce consistent quality drug product is deemed adequate.

(b) (4)

On the basis of the stability data provided 24-month expiration dating period was proposed and deemed well justified when stored in a refrigerator between 2°C and 8°C (36°F and 46°F) in the proposed container closure system. Once opened, the bottle can be stored at room temperature for up to 28 days in the carton.

The identity, strength, purity and quality of the drug product are assured by adequate raw material controls, validated manufacturing process and drug product specification.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	SYNDROS
Non Proprietary Name of the Drug Product	Dronabinol solution
Non Proprietary Name of the Drug Substance	Dronabinol
Proposed Indication(s) including Intended Patient Population	a) Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. b) Anorexia associated with weight loss in patients with AIDS
Duration of Treatment	As needed
Maximum Daily Dose	Anorexia Associated with weight loss in adult patient with AIDS: • (b) (4) (2.125 mg) orally twice daily, one hour before lunch and supper. Nausea and vomiting associated with chemotherapy in adult patients who failed conventional antiemetics: • starting dose of (b) (4) (4.25 mg), administered 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. (b) (4)

	(b) (4) .
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Application Technical Lead Signature:
From the quality perspective this NDA is **not** deemed ready for approval at this time in its present form per 21 CFR 314.125 (b)(6), until the label/labeling issues are satisfactorily resolved **(see the List of Deficiencies on p. 99).**

Hitesh Shroff, Ph.D.
Application Team Lead, Branch V
Division of New Drug products II
02/26/2016

Hitesh N. Shroff -S

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I concur with the reviewer's recommendation.

Juandria Williams, PhD; DIA/B3
2/18/2016

Juandria Williams -S
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ASSESSMENT OF THE BIOPHARMACUETICS

21. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

22. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Dronabinol capsule is currently marketed under trade name Marinol and also as generic dronabinol capsules. It is indicated for the treatment of anorexia associated with weight loss in patients with AIDS, and for nausea and vomiting associated with cancer chemotherapy.

In this current submission, the Applicant developed dronabinol oral solution to provide a dronabinol formulation readily deliverable for patients with swallowing problems. The proposed drug product uses the currently approved Marinol capsules as the reference drug.

Reviewer's Assessment:

Three formulations have been developed by the Applicant during the clinical development program. The summaries for the lots numbers used in each of the clinical programs are shown in Table 1.

Table 1. Summary of Lots Used in Clinical Studies of Dronabinol Oral Solution

Study Number	Clinical Phase	Formulation of Dronabinol	Lot Numbers
INS-06-006	1	Aqueous Dronabinol Oral Solution	074I0307
		(b) (4)	
INS-08-008	1	Aqueous Dronabinol Oral Solution 0.541% w/w (Final Formulation)	805588
		(b) (4)	805587

Study Number	Clinical Phase	Formulation of Dronabinol	Lot Numbers
INS-10-012	1	Aqueous Dronabinol Oral Solution 0.541% w/w (Final Formulation) [b]	100310
INS-12-015	1	Aqueous Dronabinol Oral Solution 0.541% w/w (Final Formulation) [b]	100310

a (b) (4)

b

c

The development for dronabinol oral solution (lot# 074I037) was discontinued due to its (b) (4). The formulation used in INS-08-008 was selected for further development and determined to be the final formulation, and was used in clinical studies INS-08-008, IND-10-012, and IND-12-015. The composition for this formulation is shown in Table 2.

Table 2. Composition of the To-Be-Marketed Dronabinol Oral Solution

Component	Function	Composition	
		%, (w/w)	mg/mL[a]
Dronabinol	Active Ingredient	0.541	5.00
Butylated hydroxyanisole (BHA)	(b) (4)	0.010	0.09
Sucralose	Sweetener	0.050	0.46
Methylparaben	Preservative	0.020	0.18
Propylparaben	Preservative	0.020	0.18
PEG 400	Co-solvent	12.000	110.91
Propylene glycol	Co-solvent	5.500	50.83
Water	Solvent/Diluent	31.859	294.45
Dehydrated alcohol	Co-solvent	QS to 100.000 % (corresponds to about 50.000%)	QS to 1.00 mL (corresponds to about 462.11 mg)

(b) (4)

Total	100.000%	1.00 mL

(b) (4)

Table 3 describes batch identification information, including production scale, package

size, and batch use in the dronabinol oral solution development program.

Table 3. Description of clinical and stability batches of Dronabinol Oral Solution

Lot No.	805588	100310	200482	200483	300266	400248
Concentration	5mg/mL	5mg/mL	5mg/mL	5mg/mL	5mg/mL	5mg/mL
Manufacturing site	DPT Lakewood	DPT Lakewood	DPT Lakewood	DPT Lakewood	DPT Lakewood	DPT Lakewood
Manufacturing date	August 13, 2008	April 12, 2011	September 24, 2012	September 26, 2012	April 15, 2013	April 8, 2014
Batch size	(b) (4)					
Drug substance Lot number[a]	D9021208-02	D9092910-01	D9042612-01	D9042712-01	D9030513-01	D9092713-01
Use	Clinical[b]/ Supportive Stability	Clinical[c]/ Stability	Manufacturing Development	Stability	Clinical[d]/ Stability	Stability

[a] Manufacturer (b) (4)
[b] Clinical Study INS-08-008
[c] Clinical Studies INS-10-012 and INS-12-015
[d] Clinical Study INS-13-017 (Abuse Potential Study)

Since this is an oral solution product, there is no dissolution method development program in the submission. To support the dronabinol oral solution, four pharmacokinetic studies were conducted by the Applicant. These studies are: "a proof of concept, ascending dose study using a dronabinol syrup formulation to evaluate safety, tolerability and pharmacokinetics (INS-06-006)"; "a single-dose crossover study to evaluate the pharmacokinetic profile and comparative bioavailability of dronabinol syrup 10 mg, dronabinol oral solution 10 mg, and Marinol® Capsules 10 mg (INS-08-008)"; "a single-dose replicate-crossover study of comparative bioavailability of dronabinol oral solution 5 mg versus Marinol® Capsules 5 mg (INS-10-012)"; and "a pivotal comparative bioavailability trial of the final, to-be-marketed formulation of Dronabinol Oral Solution 4.25 mg versus Marinol® Capsules 5 mg (INS-12-015)". Office of Clinical Pharmacology would review all these clinical studies.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The proposed drug product is dronabinol oral solution, which is neither reconstituted nor diluted for use. There is no dissolution method development for this drug product, and the to-be-marketed formulation has been used in clinical studies, INS-08-008, IND-10-012, and IND-12-015.

The review of these clinical studies would be conducted by Office of Clinical Pharmacology. From the Biopharmaceutics perspective, NDA 205525 is recommended for approval.

Peng (Vincent) Duan, Ph.D.
Biopharmaceutics/ONDP/OPQ
01/26/2016

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Date: 2016.02.26 14:19:46 -05'00'

Supervisor Comments and Concurrence:

I Concur. 01/26/16

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead

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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

23. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Review of Applicant's Response:
Drug Product Specifications
Microbial enumeration and specified organism screening tests are performed per USP<61> and USP<62> under protocol number DPT-SOP-00686. The drug product specification for total aerobic microbial count is ≤ (b) (4) CFU/g and the total yeasts/molds count is ≤ (b) (4) CFU/g, including the absence of *E. coli* and *B. cepacia* complex. The applicant has provided recovery validation results for compendial microorganisms in the documents titled, "Antimicrobial

Effectiveness Testing – Dronabinol 5 mg/mL.pdf" and "Validation Report-M-11019.pdf" (Sections: 3.2.P.2 and 3.2.P.5.3, respectively; Submission date: Jun. 1, 2015). For the absence of *E. coli* and *B. cepacia*, the drug product is diluted 1:20 [10 mL with 190 mL of tryptone-azolectin-tween (TAT) broth] and 1:50 (10 mL in 490 mL of TAT broth), respectively. For microbial enumeration testing, the drug product is diluted 1:10 (10 mL with 90 mL of TAT broth). The mean weight of 10 mL of the drug product is equivalent to 9.2 g. The specification is based on the more stringent limit described in grams of drug product. The applicant provides microbial limits testing results for batch numbers 100310, 200482, 300266, 400248, and 200483. The total aerobic count and total fungal count were < (b) (4) CFU/mL, and the absence of *E. coli* and *B. cepacia* was observed for all batches. Therefore, the results are compliant with the given specification.

Stability Summary and Conclusion

The applicant is requesting a twenty-four month expiry when stored at 2 – 8°C. The shelf life specification for microbial enumeration is the same as outlined above for release of the drug product, and microbial testing is performed annually. The applicant has provided stability data for five batches manufactured using the commercial process (batch numbers 100310, 200483, 300266, 400248, and 805588). These studies were carried out under long-term conditions (5°C ± 3°C; out to 36 months). Results are provided for various time points for the different batches under long-term conditions (e.g., 36, 24, 18, 6, and 36 months, respectively). Microbial enumeration results complied with the specification for the time points tested.

Post-Approval Stability Protocol and Stability Commitment

The applicant commits to performing post-approval stability, with annual microbial limit testing, under long-term conditions (2 – 8°C) on the first three commercial production lots. Yearly thereafter, at least one production batch is placed on the stability program.

Package Insert

The storage condition is 2 – 8°C; however, once opened the bottle is stored at room temperature up to 28 days. Upon opening the bottle, the (b) (4) cap adaptor is inserted into the glass (b) (4) and remains in the glass (b) (4) for all future uses. Dosing of the drug product is performed using the provided dosing syringe.

Reviewer's Assessment:

The specification for microbial limit testing and the absence of *E. coli* is acceptable per USP<1111> for an aqueous preparation for oral use. Inclusion of the absence of *B. cepacia* further ensures minimal risk of microbial contamination of the drug product. The applicant has met regulatory expectations regarding microbial control and testing of the subject drug product. The applicant has also met the regulatory expectations

regarding microbiological tests and sampling frequencies for the stability program associated with the subject drug product. Finally, antimicrobial effectiveness testing was performed per USP<51> demonstrating the effectiveness of the preservative system for the room temperature 28 day hold following the bottle being opened. Therefore, minimal patient risk is derived from the drug product storage conditions.

Adequate

2.3.P.6 Reference Standards or Materials

24. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: The subject drug product is a non-sterile oral solution. Therefore, container-closure integrity testing is not required for this drug product class.

Reviewer's Assessment:

Adequate

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

25. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: The subject drug product does not contain materials of biological origin or derived from biological sources.

Reviewer's Assessment:

Adequate

26. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of

the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: The subject drug product does not contain materials of biological origin or derived from biological sources.

Reviewer's Assessment:

Adequate

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The Division of Microbiology Assessment has reviewed NDA 205525 for Dronabinol Oral Solution, and found the microbiology information acceptable. From a microbiology perspective, NDA 205525 is recommended for **APPROVAL.**

Jonathan G. Swoboda, PhD
Microbiology Reviewer
OPQ/OPF/Division of Microbiology Assessment Branch 3

Jonathan Swoboda -S
Digitally signed by Jonathan Swoboda -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013691470, cn=Jonathan Swoboda -S
Date: 2016.02.29 13:17:47 -05'00'

Supervisor Comments and Concurrence:

I concur with the microbiology assessment. NDA 205525 is recommended for **APPROVAL.**

John W. Metcalfe, PhD
Quality Assessment Lead (Acting)
OPQ/OPF/Division of Microbiology Assessment Branch 3

John W. Metcalfe -A
Digitally signed by John W. Metcalfe -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300198103, cn=John W. Metcalfe -A
Date: 2016.02.29 14:41:08 -05'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant claimed a categorical exclusion from the requirement of an environmental assessment because:

1. While the action is expected to increase the use of the product's active moiety, the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb (25 CFR 25.31(b)) and
2. To the best of the applicant's knowledge, no extraordinary circumstances exist (25 CFR 25.15(d)).

Reviewer's Assessment: The claimed categorical exclusion from the preparation of an environmental assessment (EA) based on the calculated EIC ((b) (4) ppt<< 1ppb) and the absence of extraordinary circumstances is in accordance with 21 CFR 25.31, and is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The claimed categorical exclusion from the preparation of an Environmental Assessment (EA) per 21 CFR 25.31 (b) is acceptable.

Reviewer's Signature
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP
2/20/2016

Hitesh N. Shroff -S
Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2016.02.29 12:13:03 -05'00'

Secondary Review Comments and Concurrence:
I concur.

Supervisor's Signature
Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP
02/24/2016

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.02.29 13:30:10 -05'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Carton and Container Labels

Immediate container labels

30 mL Bottle Label

(b) (4)

[redacted]

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug name is not presented correctly. **Not Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed as (b) (4) [redacted] **Not Satisfactory**
Net contents (21 CFR 201.51(a))	Net content properly displayed as 30 mL **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is indicated properly. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Displayed properly **Satisfactory**
Storage conditions	Storage condition is not displayed properly **Not Satisfactory**
Bar code (21CFR 201.25)	Barcode is displayed. **Satisfactory**
Name of manufacturer/distributor	The names of manufacturer for and by are displayed correctly. **Satisfactory**
List of Ingredients	Ingredients are not listed. **Not Satisfactory**

Evaluation: Not adequate. The 30 mL bottle label should be revised to include the following information:

- The drug name should be displayed as below:

  TRADENAME
  (dronabinol) solution
  [redacted] (b) (4)

- Delete the strength statement "5 mg/mL"
- Revise the storage statement as shown below:

  [redacted] (b) (4) between 2°C and 8°C (36°F and 46°F). Once opened, the bottle can be stored at room temperature [redacted] (b) (4).

- Display the following statement describing the route of administration :

  For oral administration only

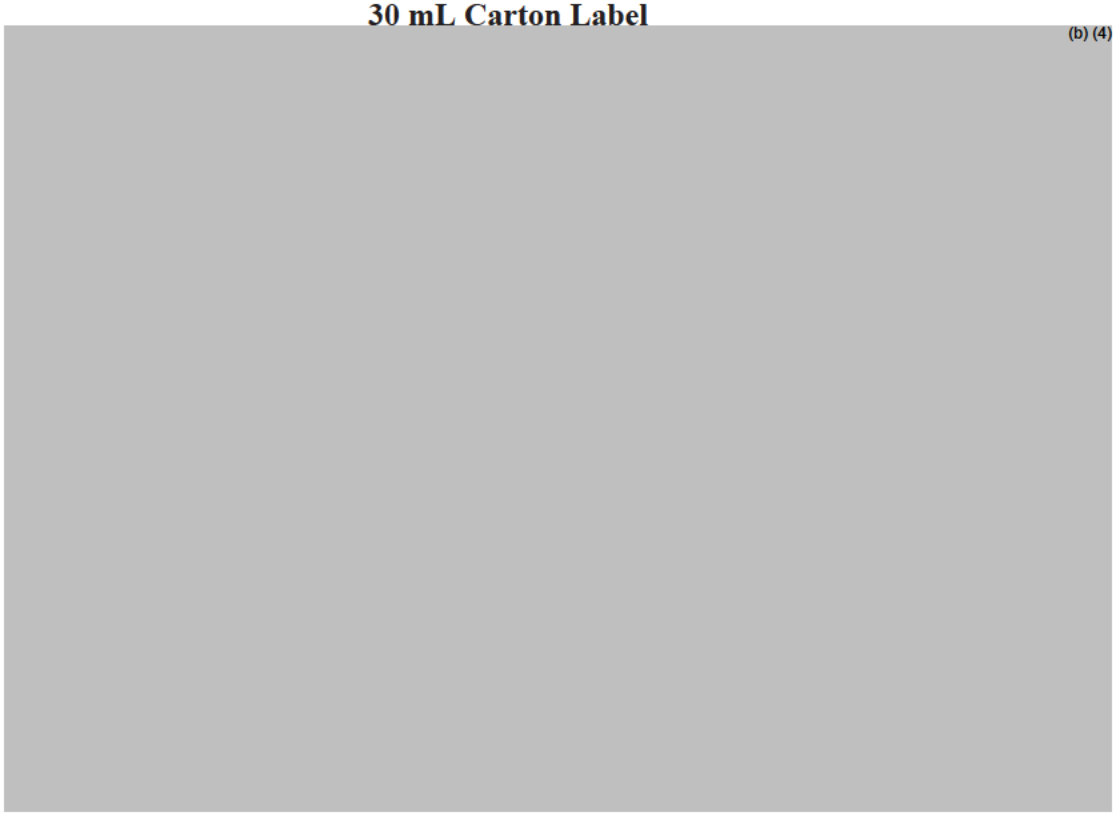
- Revise the ingredients list statement as shown below:

  Each [redacted] (b) (4) TRADENAME contains [redacted] (b) (4) mg dronabinol, [redacted] (b) (4) % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.

Carton labels

30 mL Carton Label

(b) (4)



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The drug name is not presented correctly. **Not Satisfactory**
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Displayed as (b) (4) **Not Satisfactory**
Net quantity of dosage form (21 CFR 201.51(a))	Correctly Displayed on the carton. **Satisfactory**
"Rx only" displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed on the carton. **Satisfactory**
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Lot and Exp are displayed. **Satisfactory**
Storage conditions	Storage conditions not described properly on the carton. **Not Satisfactory**
Bar code (21CFR 201.25)	Bar code displayed correctly **Satisfactory**
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number displayed correctly **Satisfactory**
Manufacturer/distributor's name 21CFR201.1(a)	The names of manufacturer for and by are displayed correctly. **Satisfactory**

The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	The ingredients are not listed. **Not Satisfactory**
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information" (21 CFR 201.55)	This statement is correctly displayed as "See accompanying package insert for full prescribing" information" **Satisfactory**
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	Not Displayed. Not required for Rx drugs **Satisfactory**
Route of Administration (21 CFR 201.100(b)	Described as "oral solution" **Satisfactory**

Evaluation: Not Adequate. The 30 mL bottle carton label should be revised to include the following information:

- The drug name should be displayed as below:
  TRADENAME
  (dronabinol) solution
  [redacted] (b) (4)
- Delete the strength statement "5 mg/mL"
- Revise the storage statement as shown below:
  [redacted] (b) (4) between 2°C and 8°C (36°F and 46°F). Once opened, the bottle can be stored at room temperature [redacted] (b) (4).
- Revise the ingredients list statement as shown below:
  Each [redacted] (b) (4) TRADENAME contains [redacted] (b) (4) mg dronabinol, [redacted] (b) (4) % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.
- Display the following statement describing the route of administration :
  For oral administration only

- **Labeling Review**

The following is a summary of the labeling review.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME (dronabinol) oral solution, (b) (4)
Initial U.S. Approval: 1985

DOSAGE FORMS AND STRENGTHS
Oral solution: (b) (4) (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name Dosage form, route of administration Controlled drug substance symbol (if applicable)	TRADENAME (dronabinol)oral solution, (b) (4)	The drug product title is not described correctly. **Not Satisfactory**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Oral solution: (b) (4)	The dosage form and strength are not described correctly. **Not Satisfactory**
Whether the drug product is scored (If the product is not scored, do not say "not scored.")		The product is not scored. **Satisfactory**

Evaluation: Not adequate. This section should be revised as follows:

- The drug product title should be as shown below:
  TRADENAME (dronabinol) solution, for oral use, (b) (4)
- The dosage forms and strength section should be revised as follows:
  Solution: (b) (4)

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

(b) (4) a clear pale yellow to brown solution (b) (4)
(b) (4)

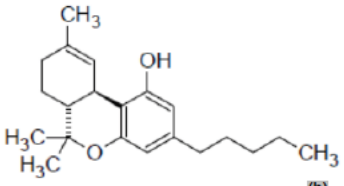
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Solution	Dosage form is described correctly. **Satisfactory**
Strengths: in metric system	(b) (4)	The strength is described correctly. **Satisfactory**
Description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear pale yellow brown solution	The dosage form is described correctly. **Satisfactory**

Evaluation: Adequate.

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol. Dronabinol has the following empirical and structural formulas:

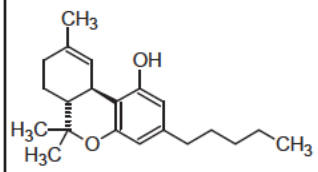


(b) (4)
$C_{21}H_{30}O_2$ (molecular weight=314.4

(b) (4)

(b) (4) Dronabinol is insoluble in water (b) (4)
(b) (4) It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

(b) (4)
(b) (4) the following inactive ingredients: dehydrated alcohol, PEG 400, propylene glycol, sucralose, methylparaben, propylparaben and butylated hydroxyanisole.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADENAME Dronabinol	The proprietary name and establish name are not displayed correctly. **Not Satisfactory**
Dosage form and route of administration	(b) (4)	Dosage form and route of Administration are not displayed correctly. **Not Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	**Not applicable**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Dehydrated alcohol, PEG 400, propylene glycol, sucralose, methylparaben, propylparaben and butylated hydroxianisole	Information for inactive ingredients is not provided correctly. **Not Satisfactory**
Statement of being sterile (if applicable)	Not applicable	**Not applicable**
Pharmacological/ therapeutic class	Cannabinoid	The Pharmacological/ therapeutic class displayed correctly **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol Molecular formula: $C_{21}H_{30}O_2$ Molecular weight: 314.46 molecular structure is: 	The chemical name, molecular formula, molecular weight and molecular structure are correct. **Satisfactory**
If radioactive, statement of important nuclear characteristics.		Not applicable

Other important chemical or physical properties (such as pKa, solubility, or pH)	Dronabinol is a [(b) (4)] Dronabinol is insoluble in water [(b) (4)] It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.	The DS is described correctly. **Satisfactory**

Evaluation: Not adequate. This section should be revised as follows:

- Revise the DP description as shown below:
  Each [(b) (4)] mL of TRADENAME [(b) (4)] contains [(b) (4)] mg of dronabinol and the following inactive ingredients: [(b) (4)] % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.
- Replace the statement [(b) (4)] with the following statement:
  Dronabinol is a clear colorless to amber oil.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

- TRADENAME is supplied in a clear, amber-colored glass bottle [(b) (4)] [(b) (4)] oral syringe, and a push-in bottle adapter.
- NDC 20482-335-30 - (30 mL [(b) (4)] bottle, oral syringe, and a push-in bottle adapter). [(b) (4)]
- Store in a refrigerator between 2° and 8°C (36° and 46°F). [(b) (4)] [(b) (4)]
- [(b) (4)]

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	[(b) (4)]	The strength is described correctly. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	30 mL [(b) (4)] bottle	This information should be revised **Not Satisfactory**

Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not provided	This information is not provided. NDC number is provided. **Not Satisfactory**
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Special storage condition is provided.
Storage conditions	Store in refrigerator between 2° and 8° (36° and 46 °F). (b) (4) .	Information is provided. **Satisfactory**

Evaluation: Not adequate. 16. How Supplied and Handling section should be revised as follows:

- The following drug product and container closure description should be added
  TRADENAME solution is a clear pale yellow to brown solution. It is supplied in a multi-dose clear amber 30 mL glass bottle. It is capped with a 20 mm child-resistant white polypropylene screw cap with a Teflon coated liner. (b) (4) The bottle is wrapped with a polyvinyl chloride body band to provide temper evidence and packaged in a carton with a graduated oral dispenser and a press-in bottle adapter.
- Revise the "NDC……" statement as shown below:
  NDC 20482-335-30 30-mL multi-dose bottle, oral syringe and push-in adapter
- Place the statement (b) (4) at the end of the storage description.
- Remove the statement (b) (4)

- Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured by:
DPT (b) (4) LLC, Lakewood, NJ, 08701
For:
Insys Therapeutics, Inc., Chandler, AZ 85286

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: (b) (4)	Information is correctly provided. **Satisfactory**

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: NOT Adequate.

The applicant has provided preliminary labels and package insert, and they have not been finalized as of this review. The comments for revision should be resolved during the labeling discussions with the applicant.

Reviewer's Signature
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP
2//24/2016

Hitesh N. Shroff -S
Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2016.02.29 12:14:43 -05'00'

Secondary Review Comments and Concurrence:
I concur.

Supervisor's Signature
Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II/ONDP
XX/XX/2016

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.02.29 13:28:30 -05'00'

II. List of Deficiencies To Be Communicated

A. Regarding Label/labeling

1. PI

"Highlights" Section
This section should be revised as follows:

- The drug product title should be as shown below:
  TRADENAME (dronabinol) solution, for oral use, (b) (4)

"Dosage Forms and Strength" Section
This strength section should be revised as follows:

- The dosage from and strength should be as shown below:
  Solution: (b) (4)

#11 Description

This section should be revised as follows:

- Revise the DP description as shown below:
  Each (b) (4) mL of TRADENAME (b) (4) contains (b) (4) mg of dronabinol and the following inactive ingredients: (b) (4) % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.
- Replace the statement (b) (4) with the following statement:
  Dronabinol is a clear colorless to amber oil.

#16 How supplied/storage and handling

This section should be revised as follows:

- The following drug product and container closure description should be added:
  TRADENAME solution is a clear pale yellow to brown solution. It is supplied in a multi-dose clear amber 30 mL glass bottle. It is capped with a 20 mm child-resistant white polypropylene screw cap with a Teflon coated liner. (b) (4) The bottle is wrapped with a polyvinyl chloride

body band to provide temper evidence and packaged in a carton with a graduated oral dispenser and a press-in bottle adapter.

- Revise the "NDC……" statement as shown below:
  NDC 20482-335-30 30-mL multi-dose bottle, oral syringe and push-in adapter
- Place the statement [redacted] (b) (4) at the end of the storage description.
- Remove the statement [redacted] (b) (4)

2. Labels

Immediate container labels:

The 30 mL bottle label should be revised to include the following information:

- The drug name should be displayed as below:
  TRADENAME
  (dronabinol) solution
  [redacted] (b) (4)
- Delete the strength statement "5 mg/mL"
- Revise the storage statement as shown below:
  [redacted] (b) (4) 2°C and 8°C (36°F and 46°F). Once opened, the bottle can be stored at room temperature [redacted] (b) (4).
- Display the following statement describing the route of administration :
  For oral administration only
- Revise the ingredients list statement as shown below:
  Each [redacted] (b) (4) mL TRADENAME contains [redacted] (b) (4) mg dronabinol, [redacted] (b) (4) % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.

Carton labels:

The 30 mL bottle carton label should be revised to include the following information:

- The drug name should be displayed as below:
  TRADENAME
  (dronabinol) solution
  [redacted] (b) (4)
- Delete the strength statement "5 mg/mL"

- Revise the storage statement as shown below:
  [redacted] between 2°C and 8°C (36°F and 46°F). Once opened, the bottle can be stored at room temperature [redacted].
- Revise the ingredients list statement as shown below:
  Each [redacted] mL TRADENAME contains [redacted] mg dronabinol, [redacted] % dehydrated alcohol, polyethylene glycol 400, propylene glycol, sucralose, methyl paraben, propyl paraben, butylated hydroxyanisole and water.
- Display the following statement describing the route of administration :
  For oral administration only

III. Attachments

A. Facility

Establishment Name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)		CSN; Drug substance manufacturer packaging, and labeling	Last inspection: (b) (4) VAI	Low risk	Acceptable
Insys Therapeutics, Inc.	3011419064	CTL; Drug substance testing for release and stability	Recent PAI in January 2016 NAI	**High risk.** No previous inspectional history	Acceptable
DPT Lakewood LLC	2242829	LIQ; Drug product manufacture, (b) (4) , packaging and labeling, analytical release, and alternative stability testing site	Last inspection: (b) (4) NAI (Profile LIQ not covered) Previous inspection: (b) (4) NAI (Profile LIQ)	**Low Risk**	Per DO recommendation, acceptable based on file review.
Insys Therapeutics, Inc.	3006646520	CTL; Analytical release and stability testing	Last inspection: 31-Jan-2014 NAI (Profile CTL)	**Low risk**	Acceptable based on profile.

OVERALL RECOMMENDATION: "Approve" recommendation was entered in Panorama on February 18, 2016

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications

No active OAI / POAI Alerts are present against the facilities on selected Projects

Refresh

Facility Status View for NDA 205525

Displays information for the facilities that are associated to NDA 205525 . It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OP
Time run: 2/20/2016 7:31:37 PM

Overall Manufacturing Inspection Recommendations for NDA 205525

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing I Task Co
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	INSYS DEVELOPMENT CO INC	Approve	Complete	2/18/2016
NDA 205525-Orig1-New/NDA(1)	INSYS THERAPEUTICS INC	Pending	New	
NDA 205525-Orig1-Resubmission/After	INSYS DEVELOPMENT		Not Applicable	9/2/2015

Facility Status View for NDA 205525

Displays information for the facilities that are associated to NDA 205525 . It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
Time run: 2/20/2016 7:31:37 PM

Overall Manufacturing Inspection Recommendations for NDA 205525

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	INSYS DEVELOPMENT CO INC	Approve	Complete	2/18/2016
NDA 205525-Orig1-New/NDA(1)	INSYS THERAPEUTICS INC	Pending	New	
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	INSYS DEVELOPMENT CO INC		Not Applicable	9/2/2015

OPF Facility Recommendations for Facilities on NDA 205525

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	3011419064	079613643	INSYS THERAPEUTICS, INC	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/18/2016
NDA 205525-Orig1-New/NDA(1)	(b) (4)			CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Pending	New	
NDA 205525-Orig1-Resubmission/After Refusal to File(4)				CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Approve Facility	Complete	2/18/2016
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	3009646526	803052443	INSYS THERAPEUTICS INC	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	7/13/2015
NDA 205525-Orig1-New/NDA(1)	3009646526	803052443	INSYS THERAPEUTICS INC	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	10/7/2014
NDA 205525-Orig1-New/NDA(1)	2242829	077744035	DPT LAKEWOOD LLC	LIQ NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS)	Pending	New	
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	2242829	077744035	DPT LAKEWOOD LLC	LIQ NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS)	Approve Facility	Complete	7/13/2015
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	(b) (4)					Cancelled	6/29/2015
NDA 205525-Orig1-Resubmission/After Refusal to File(4)	(b) (4)			LIQ NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS)		Cancelled	6/4/2015

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B. Lifecycle Knowledge Management

a) Drug Product

Risk Assessment:

Risk Assessment for dronabinol solution, 4.25 mg/0.85 mL

Product attribute/CQA	Factors that can impact the CQA	FMECA RPN Number	Risk Mitigation Approach	Risk Evaluation	Final Risk
Assay, stability	• Formulation Container closure • Raw materials • Process parameters • Scale/equipment • Site	Release (6) stability (18)	The proposed DP manufacturing process includes IPC to consistently produce quality DP. The DS assay is determined by a validated HPLC method. The long term and accelerated stability testing results demonstrated that the DP is stable up to 24 months when refrigerated.	The DP is expected to be safe and effective during 24-month shelf life period from quality perspective.	Low to None
Impurities/related substances (b) (4)	• Formulation • Excipient change • Process parameters • Scale/equipment • Site	27 27	The impurities are controlled by DS specification and DP specification at release and stability. The impurities are assessed by validated HPLC methods.	The impurities in the DP are within the specification in the registration batches.	Low to None
Dosing accuracy	• dosing device • Formulation • Process parameters • Scale/equipment • Site	6	The oral dispenser is graduated to deliver precise amount of DP.	The oral dispenser is acceptable.	Low to None
Palatability	• Formulation • excipient change • Process parameters • Scale/equipment • Site	45 45	The target quality product profile is tailored to the patients. The DP is supplied in amber bottle with an adapter and an oral dispenser. The maximum dosage is (b) (4) . Sucralose is added as a sweetener.	The drug product is tailored to be palatable to the patient population.	Low to None

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date:

Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 7/01/2016 10:25:07AM
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