

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205525Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 20, 2016
From	Joette M. Meyer, PharmD. Associate Director for Labeling Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 205525
Applicant	Insys Therapeutics, Inc.
Date of Submission	August 12, 2014 (Refuse to File) June 1, 2015 (Resubmission)
PDUFA Goal Date	April 1, 2016 (extended to July 1, 2016 by a major amendment submitted March 10, 2016).
Proprietary Name / Non-Proprietary Name	Syndros®/Dronabinol
Dosage form(s) / Strength(s)	Oral solution 5 mg/mL; 30 mL multiple-unit container
Applicant Proposed Indication(s)/Population(s)	<ul style="list-style-type: none"> • Anorexia associated with weight loss in patients with AIDS; and • Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
Recommendation on Regulatory Action	Approval, pending final labeling, including Prescribing Information, Patient Information, Instructions for Use and carton/container labeling; and inspection of the finished drug-device manufacturing site. Discussions on the scheduling of this product under the Controlled Substances Act are ongoing.
Recommended Indication(s)/Population(s) (if applicable)	<ul style="list-style-type: none"> • Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS); and • Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

EDR Location: <\\CDSESUB1\evsprod\NDA205525\205525.enx>

1. Introduction

This is a resubmission of a 505(b)2 NDA for dronabinol oral solution (SYNDROS®). The NDA references the approved drug, Marinol® (dronabinol capsules; NDA 18651; approved May 31, 1985) as the listed drug. The original submission of this NDA dated August 12, 2014 received a Refuse-to-File letter on October 10, 2014 citing ‘failure to address the requirements under the Pediatric Research Equity Act’ as the sponsor did not have an agreed initial

Pediatric Study Plan (iPSP) prior to NDA submission. Prior to NDA resubmission, on May 19, 2015, the sponsor received an agreed iPSP letter (filed under the IND 75,228).

Dronabinol is a synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (marijuana).

Dronabinol oral solution is proposed to-be-marketed in a clear, amber-colored glass bottle with a fill volume of 30 mL containing 150 mg of dronabinol (5 mg/mL). The solution is co-packaged with a press-in bottle adapter and an oral dispenser (syringe) marked with the graduations allowing the measurement of prescribed doses.

The development program for dronabinol oral solution included five clinical pharmacology studies and a human abuse potential study.

The sponsor is relying on the summary findings of safety and effectiveness for Marinol capsules (NDA 18651) for the indications of:

- Anorexia associated with weight loss in patients with AIDS; and
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Therapeutic Alternatives

Appetite Stimulants¹

Over the past decade, significant advancement has been made in the treatment of HIV. However, some HIV-infected patients may continue to experience weight loss at some time during the course of the disease, especially in the later stages of the disease (e.g. AIDS).

The principle management of involuntary weight loss is to identify and treat the etiology of the weight loss. Therapeutic attention to reversing weight loss without addressing the etiology has not been shown to improve the overall prognosis. Causes of weight loss can vary from inadequate nutrition due to anorexia or poverty, to malabsorption, disturbances of metabolism (e.g. hyper-metabolic state), or infections.

The management of gradual HIV-associated weight loss and AIDS wasting syndrome are complex and multi-disciplinary. Generally, initiation of successful HAART or optimizing the current HAART regimen leads to improved weight gain. Furthermore, improved nutritional supplement and exercise are also recommended. After evaluating for conditions which may be contributing to the weight loss, specific therapies are implemented to reverse the weight loss. These include treating opportunistic infections, reducing nausea and/or vomiting, treating the anorexia and the changes in metabolism.

The initial evaluation of patients with anorexia should include review of medications whose adverse effects may include anorexia. In addition to medical evaluations for causes of

¹ Adapted from clinical consult review by Yodit Belew MD, Division of Antiviral Drug Products, entered in DARRTS January 21, 2015 under IND 75228, in response to the sponsor's Pediatric Study Plan.
CDER Cross Discipline Team Leader Review Template 2015 Edition
Version date: June 9, 2015. For initial rollout (NME/original BLA reviews)

anorexia, psychological evaluation is also important to assess for non-organic etiologies of anorexia.

After completing the complex steps of evaluations and treatments for weight loss, if no improvement in weight gain is observed, pharmacological therapies may be used to either directly stimulate appetite (e.g. dronabinol) or lead to weight gain through other mechanisms (e.g. steroid or hormonal therapies).

There is no standardized approach with selection of drugs for stimulating appetite.

Megestrol (Megace®) is FDA approved for treatment of anorexia, cachexia, or an unexplained, significant weight loss in adult patients with AIDS. Because, megestrol can lower the serum testosterone levels, male patient receiving megestrol may become hypogonadal. In addition, there is a potential for adrenal insufficiency when long-term use of megestrol is discontinued. Several other hormonal (steroids) therapies are also utilized to increase total body weight. However, no steroids are FDA approved for the treatment of anorexia or weight gain in AIDS patients.

Antiemetics

Antiemetics are given for the prevention of nausea and vomiting induced by cancer chemotherapy. Treatment guidelines recommend various agents depending on the emetic risk category of the chemotherapy.²

- High risk: NK₁ receptor antagonist, 5-HT₃ receptor antagonist (or combined NK₁ receptor antagonist/5-HT₃ receptor antagonist), and a corticosteroid
- Moderate risk: 5-HT₃ receptor antagonist, and a corticosteroid
- Low risk: corticosteroid

FDA-approved NK₁ receptor antagonists include: oral aprepitant (Emend® capsules and oral suspension), injectable fosaprepitant (Emend® injection), and rolapitant (Varubi®).

Approved 5-HT₃ receptor antagonists include: oral and injectable ondansetron (Zofran®), injectable granisetron and transdermal granisetron (Sancuso®), oral and injectable dolasetron (Anzemet®), and injectable palonosetron hydrochloride (Aloxi® and others).

The only combined NK₁ receptor antagonist/5-HT₃ receptor antagonist is oral netupitant/palonosetron hydrochloride (Akynzeo®).

For emesis or nausea despite optimal prophylaxis (i.e., treatment of nausea and vomiting), the 2011 American Society of Clinical Oncology (ASCO) antiemetic clinical practice guidelines recommend clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider

² Hesketh PK, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. J Clin Oncol 2016; 34(4):381-6.

adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT₃ antagonist or adding a dopamine antagonist to the regimen.³

There are two synthetic cannabinoids approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments: dronabinol capsules (Marinol and generics) and nabilone capsules (Cesamet®). Neither product is specifically mentioned in the 2011 ASCO guidelines.

Before development of 5-HT₃ receptor antagonists and NK₁ receptor antagonists, older antiemetic agents used for prevention and treatment of nausea and vomiting associated with chemotherapy included dopamine receptor antagonists (e.g., metoclopramide) and prochlorperazine.

2. Background

Marketing History

Reference Listed Drug:

- Marinol (dronabinol capsules) approved May 31, 1985 (NDA 18651; Abbvie)

Generics:

- SVE Pharma (ANDA 78292) approved June 27, 2008
- Insys Therapeutics (ANDA 78501) approved August 19, 2011, sponsor of current NDA
- Akorn Inc (ANDA 79217), approved June 20, 2014

Regulatory Background

The following is a summary of important discussion points and advice given to the sponsor in pre-submission meetings with FDA.

End-of-Phase 2 Meeting May 13, 2010, Meeting Minutes September 20, 2010 in DARRTS (IND 75,228)

A bioequivalence study is acceptable for an NDA filing under section 505(b)(2) submission provided that the formulation used is the same as the to-be-marketed formulation.

If bioequivalence is not demonstrated between the product and the listed product, then clinical studies would be needed.

Bioequivalence does not need to be demonstrated for the active metabolite of dronabinol, 11-hydroxy-delta-9-tetrahydrocannabinol, but pharmacokinetic (PK) data should be determined for both parent and active metabolite.

A food effect study was recommended, but not required. The sponsor was asked to provide a rationale as to why a food effect study is not needed.

³ Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2011;29(31):4189-98.

Pre-NDA Meeting April 17, 2012, Meeting Minutes May 22, 2012 in DARRTS (IND 75,228)
The discussion was of the results of a comparative bioavailability study (INS-10-012) and plans for submission of a 505(b)(2) NDA.

The results of INS-10-012 indicated that for the comparison of dronabinol oral solution 5 mg to 5 mg Marinol capsule under fasted conditions bioequivalence on all PK parameters was demonstrated, except AUC which was approximately 35% higher for the oral solution.

FDA advised the sponsor that because the AUC of the product is higher than that of the listed reference product (Marinol), they would need to provide adequate safety data that support the use of the product at the highest dose for each proposed population. Or, FDA agreed that the sponsor could [REDACTED] (b) (4) conduct a new study to demonstrate the bioequivalence of their proposed product to the listed reference drug.

FDA noted that dronabinol oral solution is formulated in 50% ethanol and approximately 30% water, and may be more easily abused than Marinol (Schedule III) capsules formulated in sesame oil. The sponsor was advised to submit a proposal to address this formulation difference and justify that the abuse potential of dronabinol oral solution formulation is equal to or less than Marinol. The sponsor was cautioned that the DEA may not place the product in the same schedule as Marinol.

The sponsor was also told that if they choose to co-package a 1 mL syringe with the drug product, the 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).

Submission dated October 2, 2012, Advice Letter November 29, 2012 in DARRTS (IND 75,228)

In response to the sponsor's question regarding the need for clinical abuse liability studies, the FDA informed the sponsor that a human abuse potential study is needed and should be conducted in cannabinoid-preferring individuals at the proposed therapeutic dose, as well as at a dose that is 2-3 times the proposed therapeutic dose (if it can be tested safely), in comparison to comparable doses of Marinol. The study design should make accommodations for the pharmacokinetic differences in the two dronabinol preparations, especially with regard to the timing and duration of collection of the subjective measures.

Furthermore, given that dronabinol itself is a Schedule I substance, the product containing dronabinol would be placed into a different schedule of the Controlled Substances Act upon approval of an NDA, and the schedule would depend upon data acquired that demonstrate the abuse potential of the new product. Thus, the only way to determine whether dronabinol oral solution has an abuse potential similar to, or different from, that of Marinol (a Schedule III drug product containing oral dronabinol) is to do a direct comparison of the two products in human volunteers.

The FDA reiterated that 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 and that the study results must be included in the NDA submission for it to be considered complete.

Meeting Request dated January 8, 2013, Preliminary Comments March 7, 2013 in DARRTS (IND 75,228)

FDA provided written preliminary comments to the sponsor's questions regarding the results of a new comparative bioavailability study (INS-10-015) and the sponsor cancelled the meeting after receiving the FDA's comments.

The new study evaluated a lower dose of dronabinol oral solution, 4.25 mg, versus Marinol capsules 5 mg. Per the study results, the sponsor noted that the oral solution and Marinol capsules were bioequivalent for dronabinol with respect to C_{max} (reference-scaled approach) and with respect to AUC_{0-t} and AUC_{inf} (average bioequivalence). The sponsor also indicated that for the active metabolite, 11-OH- Δ^9 -THC, the arithmetic mean values for C_{max} , AUC_{0-t} , and AUC_{inf} were lower for the oral solution than the capsules. However, FDA previously noted that bioequivalence does not need to be established for both the parent and its metabolite.

Based on the summary provided, the FDA responded that it is reasonable to use a reference scaled approach for the analysis of bioequivalence, however, the final decision on the acceptability and adequacy of the data and analysis will be made during NDA review.

The sponsor was reminded to submit a proposal to reschedule dronabinol oral solution under the Controlled Substances Act. The proposal should address the ease with which the product can be abused by alternate routes of administration, including smoking and intravenous injection. In addition, the sponsor was advised to include a human abuse potential study.

The sponsor was advised that they must submit a Pediatric Study Plan (PSP) no later than 210 days prior to the application submission.

Protocol Submission dated August 15, 2013 (IND 75,228)

The sponsor submitted the protocol for the required human abuse potential study (INS-13-017).

Meeting Request dated August 20, 2013, Written Response December 17, 2013 in DARRTS (IND 75,228)

The sponsor requested the meeting to discuss the FDA's position that a human abuse liability study is necessary for labeling and/or scheduling, and that such a study is required for filing the NDA.

In the written response, FDA summarized the notable differences between dronabinol oral solution and Marinol capsules, for example, differences in concentration, dosage form, and composition, suggesting that the proposed oral solution product may have different abuse potential from Marinol. The proposed oral solution formulation contains 150 mg of dronabinol in 30 mL of a sweetened alcoholic solution ((b) (4) % w/w). These characteristics may increase the likelihood of abuse and unintentional overdose of the oral solution, 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 the oral solution may also be appealing to children in accidental overdose and to individuals who may intentionally abuse the product. Finally, the half-life of the 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 the 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.

FDA also provided comments and recommendations to the amendments to the human abuse protocol INS-13-017 amendments dated August 12, 2013 and August 21, 2013.

NDA Submission August 12, 2014 (NDA 205525)

The original NDA submission was submitted on this date.

Refuse to File Letter dated October 10, 2014 in DARRTS (NDA 205525)

On October 10, 2014, FDA notified the applicant that the application was not sufficiently complete to permit a substantive review. FDA refused to file the application under 21 CFR 314.101(d)(3) for failure to address the requirements under the Pediatric Research Equity Act because the applicant provided an incomplete or inadequate pediatric study plan to conduct studies to assess the safety and effectiveness of its product.

In the RTF letter the sponsor was also requested to address:

- Reports of syncope that have occurred in the interim since Marinol's approval by providing literature and discussion on the QT prolonging potential of dronabinol.
- Product Quality Microbiology issues

Teleconference held on October 14, 2014 and General Advice Letter October 30, 2014 in DARRTS (NDA 205525)

The sponsor acknowledged their error in failing to submit an agreed Pediatric Study Plan (PSP) as requested by the Agency. The sponsor agreed to submit a PSP and resubmit the application. FDA reiterated the process for submitting pediatric study plans and that in order for the sponsor to resubmit the application, FDA and the sponsor must first reach agreement on the PSP.

Pediatric Study Plan dated November 3, 2014 (IND 75,228)

The sponsor submitted their initial Pediatric Study Plan (iPSP). The iPSP was not considered acceptable and the sponsor was notified on January 30, 2015.

General Advice Letter December 10, 2014 in DARRTS (NDA 205525)

FDA refer to the October 10, 2014 RTF correspondence and requested the following issue, while not a basis for refusing to file this application, should be addressed if the application is resubmitted:

- A food-effect on the pharmacokinetics of dronabinol from the proposed formulation has not been assessed. Provide justification for not conducting this study and address

the labeling impact of the absence of this information for each of the proposed indications.

Revised iPSP dated April 20, 2015 (IND 75,228)

The sponsor submitted a revised iPSP that was agreed upon by FDA and the sponsor was notified on May 19, 2015.

NDA Resubmission June 1, 2015 (NDA 205525)

The sponsor responded to deficiencies in the RTF letter with an NDA resubmission.

NDA Information Request June 16, 2015 (NDA 205525)

FDA advised the sponsor to [REDACTED] (b) (4) deferral and partial waiver requests consistent with the pediatric development program outlined in the agreed PSP.

- For the indication of “[REDACTED] (b) (4) Nausea And Vomiting in Patients Who Failed to Respond Adequately to Conventional Antiemetics”]: deferral to study all ages.
- For the indication of “Anorexia Associated with Weight Loss in AIDS”]: deferral to study pediatric patients ages 15 to 17 years on the grounds that the product is ready for approval in adults; and a waiver to study pediatric patients ages 0 to 14 years on the grounds that studies are highly impracticable due to the small numbers.

Revised Pediatric Deferral and Partial Waiver Request June 17, 2015

The sponsor resubmitted a revised pediatric deferral and partial waiver request; however, upon review, the Division noted that the partial waiver request was not consistent with the agreed PSP dated May 19, 2015.

A teleconference was held on June 23, 2015. The sponsor acknowledged their error in failing to submit a partial waiver to study pediatric patients ages 0 to 14 years for the indication of “Anorexia Associated with Weight Loss in AIDS”. The sponsor agreed to resubmit a revised partial waiver request and replace the erroneous request. Revised waiver request submitted on June 23, 2015.

Filing Review Issues Identified August 8, 2015 in DARRTS (NDA 205525)

The sponsor was notified by FDA of a potential review issue regarding the lack of a food effect study in the NDA. The waiver request for a food effect bioavailability (BA) study was not considered acceptable. It was recommended to the sponsor they conduct a fed bioequivalence study (using Marinol as the reference formulation) to provide evidence/assurance of comparable formulation performance under fed conditions and support use of the same administration information in the Prescribing Information (PI) of the product.

The sponsor informed division on September 28, 2015 that they would conduct a fed BE study and the protocol for this study was submitted on August 24, 2015 (IND 75228).

IND Protocol Submission dated August 25, 2015, Comments October 1, 2015 in DARRTS (IND 75,288)

FDA provided comments on the sponsor's proposed protocol for the relative bioavailability study under fed conditions (INS004-15-059). FDA recommended the sponsor consider adding a third arm to the study which would evaluate the reference product (Marinol) administered under fasting conditions. The sponsor was encouraged to include the third arm to inform appropriate dosing instructions for the oral solution, if the systemic exposure was different from Marinol under fed conditions.

3. CMC/Device

Background

Marinol and the generic dronabinol capsules manufactured by Insys, the NDA sponsor, are produced by dissolving dronabinol in sesame oil and encapsulating in soft gelatin capsules. The products are formulated in sesame oil due to dronabinol's insolubility in water. However, because of the effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation, and these formulations exhibit a very high inter-subject pharmacokinetic variability, leading to a high C_{max} in some patients and associated with CNS adverse events. As a result, doses need to be titrated based upon effect and tolerability.

Originally the sponsor formulated an oral syrup, [REDACTED] (b) (4)

[REDACTED] The to-be-marketed formulation is an aqueous oral solution formulation (containing dehydrated alcohol 50% w/w). The sponsor's scientific rationale is that an aqueous formulation would allow dronabinol to mix rapidly and uniformly in the gastrointestinal tract, thereby reducing the variability in the lag time associated with capsule disintegration, dissolution and partitioning of active agent into the gastrointestinal tract fluids. The current formulation is intended to provide ease of dose titration, and more predictable exposure to meet each individual patient's needs based on body weight, degree of emesis, duration and extent of chemotherapy course and drug-related adverse events.

According to the integrated review by the FDA Quality Review Team in the Office of Pharmaceutical Quality (OPQ):

- 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 form per 21 CFR 314.125(b)(6) and 21 CFR 314.125(b)(13), until the above issues are satisfactorily resolved.

CDTL Comments: The list of deficiencies applies to the PI, the immediate container labels, and carton labels. See complete OPQ team review by Hitesh Shroff, PhD entered in Panorama on February 29, 2016.

The OPQ suggested revisions to the PI have been incorporated, but not sent to the sponsor, as of the date of this review. See Section 12 (Labeling) of this review. OPQ comments on the carton/container labels were sent to the sponsor on March 11, 2016. The sponsor provided revised carton/container labels to address the comments on March 18, 2016. Final concurrence on the carton/container labels by OPQ is pending at the time of this review.

General Product Quality Considerations

Drug Substance

The active pharmaceutical ingredient in the drug product is Dronabinol, USP, a clear, colorless to amber glassy solid. The applicant provided an LoA to reference DMF (b) (4) for the CMC information. The DMF was reviewed and found to be adequate.

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

Drug Product

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.

CDTL Comment: The review team determined during the review cycle that the representation of the dose may increase the risk of medication errors due to the number of significant figures. A recommendation was made by the Division of Medication Errors and Prevention (DMEPA) to round the doses to the nearest tenth of a decimal point. As a result the OPQ reviewer recommended the strength of the product should be written as 5 mg/mL. The corresponding content of dehydrated alcohol is 50% (w/w) and propylene glycol content is 5.5% (w/w).

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 (b) (4) key steps: (b) (4) and impurity profile, stability and shelf-life, release specifications, etc. The drug product manufacturing process, as proposed by the sponsor, is deemed adequate.

On the basis of the stability data, a 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.

Biopharmaceutics

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 sponsor. See Section 5 (Clinical Pharmacology) of this review.

Microbiology

The sponsor is requesting a twenty-four month expiry when stored at 2 to 8°C. The shelf life specification for microbial enumeration is the same 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.

The specification for microbial limit testing is acceptable for an aqueous preparation for oral use. 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 drug product. Finally, antimicrobial effectiveness testing demonstrated 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.

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

CDTL Comment: As noted above, in the RTF Letter dated October 10, 2014, product quality microbiology issues were included, but these were not considered deficiencies. Based upon the microbiology review, these issues have been addressed.

Environmental Assessment

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

Facilities Review/Inspection:

Drug Substance

- (b) (4) (drug substance, packaging and labeling): Found to be acceptable (VAI) during inspection, (b) (4)
- Insys Therapeutics, Inc. (drug substance testing for release and stability): Found to be acceptable (NAI), January 2016

Drug Product

- DPT Lakewood LLC (drug product, (b) (4) packaging and labeling, analytical release and alternative stability testing site): Found to be acceptable, based on file review by the District Office.
- Insys Therapeutics, Inc. (analytical release and stability testing); Found to be acceptable, based on profile (Control Testing Laboratory).

CDRH Consult (Drug/Device Combination Product)

As noted above, dronabinol oral solution is packaged in a 30 mL bottle, which is co-packaged with a dispenser for oral administration. CDRH was asked to review the oral dispenser and press-in bottle adapter.

A clear graduated oral dispenser and press-in bottle adapter will be provided in the carton along with drug product and package insert. At the time of first use, the press-in bottle adapter will be fitted on to the bottle that allows the patient to draw the product using an oral dispenser with ease.

CDTL Comment: See complete reviews by Kathleen Fitzgerald dated February 24, 2016 and Sarah Mollo dated February 4, 2016 and entered into DARRTS by Maureen Dewey, on behalf of CDRH reviewers, on March 10, 2016.

Markings specific to the recommended single dose of 4.25mg in 0.85 mL and 2.125 mg in 0.425 mL are printed on the (b) (4) dispenser, same as the (b) (4) oral dispenser that was used in the pivotal bioequivalence trial (INS-12-015). Use of the oral dispenser was validated in a label comprehension study. The sponsor references DMF (b) (4) for the oral dispenser and press-in adapter by (b) (4) DMF (b) (4) contains complete device materials information.

CDTL Comment: The Label Comprehension Study was reviewed by DMEPA and concerns were raised about the potential for dosing errors as a result of the markings on the oral syringe and the corresponding doses in the Dosage and Administration of the PI. A Discipline Review letter was sent on March 11, 2016 regarding these concerns. See Section 11 (Other Regulatory Issues) in this review. During the follow-up teleconference with the sponsor on March 15, 2016, they were asked to submit a side-by-side comparison table of the performance and compatibility of the new oral dosing syringe proposed to address DMEPA's comments (i.e., remove the thick black lines for 0.425 mL and 0.85 mL and re-label the oral dispenser with 0.1 mL increments (i.e., 0.1 mL, 0.2 mL, 0.3 mL, etc.) using the smaller black lines already present, taking into account the readability of the labeled markings. Specifically, the sponsor was asked to submit a table comparing the material formulation of the device components for the original proposed oral syringe (DMF# (b) (4)) to those of the newly proposed syringe and provide a certification statement from the same supplier stating that the

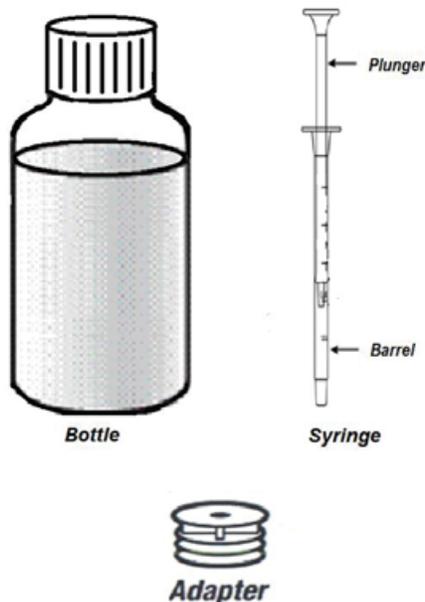
materials are identical in formulation, processing and sterilization and that no other chemicals have been added.

The sponsor's submission of March 18, 2016 addressed the comments from the Discipline Review letter regarding the biocompatibility of the original and new proposed syringe, see below.

CDRH Consult Review Addendum

On March 18, 2016, the sponsor provided revised labeling and the above requested information on the proposed new oral syringe for CDRH review. The CDHR reviewer concluded that the to-be marketed syringe and the syringe that was reviewed previously under NDA 205525 are identical in material formulation and processing. The biocompatibility and drug compatibility testing that has been performed on the syringe that was reviewed under NDA205525 (41-0236-001) can be leveraged for the evaluation of the proposed to-be marketed syringe (41-0008-163).

CDTL Comment: See addendum by Kathleen Fitzgerald dated March 21, 2016 and entered into DARRTS by Maureen Dewey, on behalf of CDRH reviewers, on March 24, 2016. The combined CDRH review by Kathleen Fitzgerald and Sarah Mollo was also updated on March 23, 2016 to reflect the new information and entered into DARRTS by Maureen Dewey, on behalf of CDRH reviewers, on March 24, 2016.



Dose Accuracy: (b) (4) oral dispenser is suitable for Dronabinol Oral Solution and allows accurate dispensing of the product.

Accessibility of Dosing/Dispensing Test: Dispensing data indicates that a minimum of 65 doses of 0.425 mL and a minimum of 33 doses of 0.85mL of dronabinol oral solution (5 mg/mL) can be accurately dispensed using the press-in adapter and oral dispenser. No compatibility issues were observed.

The review also provides the following conclusions, regarding deficiencies and information requests that were addressed during the review. The reviewer concludes that the sponsor has adequately addressed all CDRH deficiencies. The sponsor provided:

- a sample of the device components. All the components are compatible and function as intended and per the instructions for use.
- an adequate performance bench test report and results to demonstrate functionality performance of the oral dispenser/syringe and press-in adapter combination and demonstrated compatibility of the oral dispenser and press-in adapter and the number of times the adapter can be accessed by the oral dispenser.
- an adequate response to a request regarding leachables in the dispensing syringe and leachants/extractants resulting from the interaction between the drug and the press-in adapter.
- adequate information describing the nature and duration of patient contact and biocompatibility evaluation of the oral dispenser and press-in adapter evaluation.

CDRH/Office of Compliance Consult

Background

CDRH/OC was consulted to evaluate the medical device constituents of the combination product and determine if an inspection of the manufacturing facilities is warranted.

The CDRH/OC reviewer noted several deficiencies in the submission, which were addressed by the sponsor through several information requests.

CDRH/OC also recommended an inspection of the finished drug-device manufacturing site: DPT Laboratories, Ltd. DPT Lakewood, NJ site. As this is also drug product manufacturing site, CDER/OPF concurs with a post-approval inspection for the device.

CDTL Comment: See review memo by Bleta Vuniqi dated October 26, 2015 and updated February 18, 2016 and entered into DARRTS on behalf of CDRH by Maureen Dewey on March 9, 2016.

The review was updated again on March 21, 2016 to note that the application is approvable from the perspective of the applicable Quality System Requirements and entered into DARRTS on behalf of CDRH by Maureen Dewey on March 22, 2016.

A major amendment was taken on the application, which extends the action date to July 1, 2016. On April 27, 2016 OPQ requested CDRH inspect DPT Laboratories before final approval, rather than as a post-approval inspection given the extended PDUFA date.

4. Nonclinical Pharmacology/Toxicology

The sponsor did not conduct nonclinical studies and relied on the prior FDA finding of safety for dronabinol (Marinol) capsules (NDA 18651) to support the nonclinical section of the NDA. The nonclinical safety assessment was limited to the excipients and impurities in the drug substance and drug product. According to the pharmacology/toxicology reviewer, the submitted information was sufficient to provide a reasonable assurance of safety for the excipients and impurities.

CDTL Comment: See complete pharmacology/toxicology review by Fang Cai, PhD entered in DARRTS on February 22, 2016.

Excipients

All of the excipients in SYNDROS are present in oral drug formulations previously approved by the FDA and are listed in the FDA Inactive Ingredient Database. However, the estimated maximum daily intakes for BHA (2.2 mg) and dehydrated alcohol (14.5 mL) from SYNDROS are slightly higher than the maximum daily doses from approved oral drug products. In addition, the estimated maximum daily doses of sucralose (11.4 mg) and propylene glycol (1260.6 mg) exceed the maximum potencies in the FDA Inactive Ingredient Database (5.9 and 148.31 mg, respectively). Therefore, an additional safety assessment of the estimated maximum daily doses of BHA, sucralose, propylene glycol, and dehydrated alcohol was conducted by the reviewer. It was determined that the estimated maximum daily dose of BHA, sucralose and propylene glycol fall within the designated ADI (acceptable daily intake) and were not considered to be safety concerns.

The maximum daily dose of dehydrated alcohol in patients treated with SYNDROS is estimated to be 14.5 mL in a 60-kg patient, which slightly exceeds the maximum daily dose of 11 mL from approved oral drug products. However, based on Dietary Guidelines for Americans, the recommendation for alcohol consumption in moderation is up to one drink per day for adult women and two drinks per day for adult men.⁴ In the United States, a standard drink is defined as 0.6 fluid ounces of pure alcohol, equivalent to 17.7 mL of pure alcohol.⁵ Therefore, the estimated maximum daily intake of alcohol (14.5 mL/day) from SYNDROS falls within the recommended limit for moderate alcohol consumption in either men or women. Thus, the estimated maximum daily intake of alcohol resulting from SYNDROS administration is not considered to be a safety concern.

Impurities

Impurity safety assessment and qualification for products containing dronabinol are generally exempt from ICH recommendations (i.e. M7, Q3A(R2), and Q3B(R2)), as the first FDA-approved drug product containing dronabinol was approved before publication of ICH guidances. The only exception is for new or unique impurities that are found present in newly developed formulations containing dronabinol. However, no such impurities have been identified in the drug product (as per the OPQ reviewer, Hitesh Shroff). Voluntary compliance

⁴ <http://www.health.gov/dietaryguidelines/2010.asp>

⁵ <http://www.cdc.gov/alcohol/faqs.htm>

with ICH qualification thresholds is an acceptable approach for justifying proposed impurity limits in the drug substance and drug product.

Drug Substance

The drug substance in SYNDROS and the drug substance in an approved generic drug product (dronabinol capsules, ANDA 78,501) (b) (4). Thus, the potential for toxicity due to impurities (either process impurities or degradants of the drug substance) is assumed to be very similar in SYNDROS and the currently marketed generic product.

Drug Product

There are five impurities with proposed acceptance criteria that exceed the ICH qualification threshold of 0.2% (ICH guidance Q3B(R2)) (b) (4). However, the proposed specification limits for the highlighted impurities in drug product do not exceed the observed levels in the reference drug, Marinol (confirmation of this was provided by the CMC reviewer, Dr. Hitesh Shroff). Therefore, these impurities are considered as qualified at the proposed specification limits.

(b) (4)

The Sponsor provided adequate justification for all other impurity specification limits in the drug substance and drug product.

Leachables

There is no safety concern for exposure to potential leachables from the primary container: a 30 mL clear amber color Type III glass bottle with a 20 mm child-resistant cap with a Teflon coated (b) (4) liner.

Safety assessment of potential leachables from the dosing device (press-in bottle adaptor and oral syringe) was conducted by CDRH. The reviewer provided the following comment to summarize the safety assessment: *“The risk assessment provided in the submission is sufficient and the results of the risk assessment suggest that there is little likelihood of adverse systemic, genotoxic, or carcinogenic effects following patient exposure to compounds extracted from the device.”*

CDTL Comment: See complete review by Sarah Mollo dated February 4, 2016 and entered into DARRTS by Maureen Dewey, on behalf of CDRH, on March 9, 2016.

Safety Issue of QT Prolongation

In response to a clinical information request regarding syncope and the potential for QT prolongation with dronabinol, the sponsor conducted a literature search on nonclinical studies

that evaluated the effects of dronabinol on ventricular repolarization. The summary information was submitted in an amendment on November 30, 2015. The sponsor concluded there is a paucity of data on the effect of dronabinol on ventricular repolarization, and that the cardiac effects of delta-9-THC *in vitro* and in animals are limited and have often been inconsistent among the reported studies. Thus, the nonclinical data do not provide useful information for evaluating the potential of delta-9-THC to affect ventricular repolarization.

CDTL Comment: For additional discussion on QT prolongation see Section 8 (Safety) of this review.

Conclusion

In summary, the pharmacology/toxicology reviewer concluded the information available from health authorities and U.S. regulations (21 CFR) provide a reasonable assurance of safety for the estimated maximum daily intake of the excipients in SYNDROS. There is also a reasonable assurance of safety for the proposed impurity limits in the drug substance and drug product. Therefore, from a nonclinical standpoint, there are no approvability issues for this NDA.

The pharmacology/toxicology review also provides labeling recommendations for Sections 8.1 and Section 13 of the Prescribing Information (PI).

CDTL Comment: See Section 12 (Labeling) of this review.

5. Clinical Pharmacology

NDA 205525, for dronabinol oral solution is acceptable from a Clinical Pharmacology perspective.

CDTL Comment: See complete clinical pharmacology review by Sandhya Apparaju, PhD and Sue-Chih Lee, PhD entered into DARRTS on March 1, 2016.

The sponsor has conducted 5 pharmacokinetic studies:

INS-06-006

A Single Site, Randomized, Ascending Dose Study to Determine the Pharmacokinetics, Safety and Tolerability of Dronabinol Syrup in Healthy Volunteers under Fasted Conditions.

This was a randomized, placebo-controlled, single-blind sequential ascending dose, 4-sequence study to compare the relative bioavailability of ascending doses of dronabinol oral syrup (5 mg/mL) under fasting conditions in 32 healthy subjects.

- Results: The syrup formulation demonstrated dose-dependent bioavailability.

CDTL Comment: As noted previously, the syrup formulation was not pursued further (b) (4). This study was not reviewed by the clinical pharmacology team.

INS-08-008

A Pilot, Pharmacokinetic Profile and Comparative Bioavailability Study of Dronabinol Syrup 10 mg, Dronabinol Oral Solution 10 mg and Marinol (Dronabinol) Capsules 10 mg under Fasted Conditions.

This was a single-dose, 3-period, 3-sequence crossover pilot study to compare the pharmacokinetic profile and comparative bioavailability of 10 mg of dronabinol in two test formulations (oral syrup and oral solution, original solution, not the to-be-marketed) compared with 10 mg of Marinol capsules, the RLD, in 18 healthy subjects under fasted conditions.

- Results: the oral syrup and the oral solution were not bioequivalent to each other or to the equivalent strength of Marinol capsules.

CDTL Comment: The oral solution in this study was not the to-be-marketed formulation. Therefore, this study was not the primary focus of the clinical pharmacology review.

INS-10-012

A Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 5 mg versus Marinol Capsules 5 mg Under Fasted Conditions.

This “pivotal” study was a single-dose, open-label, randomized, 4-period, two-treatment, two-sequence replicate design crossover study in which 88 healthy adult subjects were scheduled to receive four separate single-dose administrations of 5 mg dronabinol oral solution (final to-be-marketed) or Marinol capsules in four study periods.

- Results: the oral solution (to-be-marketed formulation) was not bioequivalent to the equivalent strength of Marinol capsules. However, When AUC_{∞} was dose-adjusted from 5 mg to match the administration of 4.25 mg dronabinol oral solution, the predicted dose-adjusted AUC_{∞} and the observed AUC_{∞} were very similar (3.81 ng•hr/mL and 3.84 ng•hr/mL, respectively).

CDTL Comment: This study did not demonstrate bioequivalence between 5 mg of dronabinol oral solution and 5 mg of Marinol capsules; therefore, Study INS-12-015 was conducted. The results of this study (IND-10-012) are not the primary focus of the clinical pharmacology review.

INS-12-015

A Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 4.25 mg versus Marinol Capsules 5 mg under Fasted Conditions.

This was considered one of two pivotal trials by the clinical pharmacology team (see also INS004-15-059 below).

The trial was designed as a single-dose, open-label, randomized, 4-period, two-treatment, two-sequence replicate design crossover study in which 52 healthy adult subjects were scheduled to

receive four separate single-dose administrations of 4.25 mg dronabinol oral solution (final to-be-marketed) or 5 mg Marinol capsules in four study periods under fasting conditions.

In this trial plasma concentrations of dronabinol and its active metabolite were assayed using a validated LC-MS/MS method. The performance of calibration standards, QCs, and results of the incurred sample reproducibility test for each clinical trial were within acceptable ranges.

CDTL Comment: The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data for the pivotal bioequivalence trials in NDA 205525 without an on-site inspection. See Section 11 (Other Regulatory Issues) of this review.

Relative bioavailability (dronabinol oral solution vs. Marinol capsule) results under fasted dosing conditions:

- Parent drug, dronabinol (delta-9-THC): In healthy subjects under fasted dosing conditions, dronabinol oral solution at a dose of 4.25 mg (in 0.85 mL) provided bioequivalent systemic exposures (C_{max} , AUC_1 and AUC_{inf}) of parent dronabinol (delta-9-THC) compared to approved Marinol capsule 5 mg.

Reference-scaled BE analyses was used as the within subject PK variability (sWR) for reference drug exceeded 0.294 with regard to all three PK parameters. The bioequivalence criteria were met i.e. test to reference geometric mean ratios (GMR) were within 0.8-1.25 and the criteria bounds were less than zero for the three PK parameters tested. Hence the analysis supports bioequivalence of the test and reference dronabinol products with respect to parent dronabinol, under fasted conditions.

Statistical summary for the parent drug (dronabinol; delta-9-THC)

Parameter	T/R Ratio	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
LAUCT	0.95	0.1886051	0.4342869	-0.103484	Scaled/PE	PASS
LAUCI	0.93	0.2107749	0.4591023	-0.102459	Scaled/PE	PASS
LCMAX	0.83	0.4232008	0.6505388	-0.176975	Scaled/PE	PASS

Source: Table 3 in the clinical pharmacology review

- Active metabolite (11-hydroxy-delta-9-THC): The active metabolite exposures were comparable following the dronabinol oral solution (4.25 mg) and Marinol capsule (5 mg), although bioequivalence was not strictly met for this analyte. This is considered not critical as the dose is titrated to effect for both of the proposed indications.

BE analysis was conducted for the active metabolite 11-hydroxy-delta-9-THC, as supportive information. As the within-subject PK variability (sWR) for this analyte following the reference Marinol was < 0.294 for all PK parameters, average BE analysis was employed by the sponsor. The absence of high variability in metabolite PK (i.e. sWR < 0.294) was verified by the reviewer analysis as well using SAS 9.3.

For the active metabolite, the PK parameters failed average bioequivalence criteria modestly in that, the lower 90 % confidence bounds for exposure parameters fell somewhat below the lower regulatory BE threshold of 80 %. Given the modest differences in metabolite exposure from the dronabinol oral solution relative to Marinol capsule, and given that doses are titrated to effect for both indications, this finding doesn't appear to be clinically meaningful.

Statistical summary for active metabolite in pivotal trial INS-12-015

Parameter	Least Squares Geometric Means		Geometric Mean Ratio (%)*		Within-Subject Standard Deviation†	
	Insys	Marinol			Insys	Marinol
	Lot No. 100310	Lot No. 277967A	Estimate	90% Confidence Interval	Lot No. 100310	Lot No. 277967A
Insys Lot No. 100310 vs. Marinol Lot No. 277967A						
C _{max}	2.36	3.05	77.33	72.50 → 82.49	0.287	0.265
AUC(0-t)	9.05	10.90	82.97	77.98 → 88.28	0.214	0.218
AUC(inf)	9.67	11.53	83.92	79.02 → 89.11	0.194	0.218

Source: Table 5 in the clinical pharmacology review

INS004-15-059

Open-Label, Randomized, Single-Dose, Six-Sequence, Three-Period, Crossover Comparative Bioavailability Study of Dronabinol Oral Solution, 4.25 mg under Fed Conditions, and Marinol Capsule, 5 mg under Fed and Fasted Conditions in Healthy Volunteers

This study was considered the second of two pivotal trials by the clinical pharmacology team.

CDTL Comment: As noted in the Regulatory History section of this review, FDA recommended in the Filing Review Issues Identified letter that the sponsor conduct a fed bioequivalence study (using Marinol as the reference formulation) to provide evidence/assurance of comparable formulation performance under fed conditions. The sponsor was also encouraged to include the third arm to inform appropriate dosing instructions for the oral solution, if the systemic exposure was different from Marinol under fed conditions, as the Marinol PI doesn't contain information regarding food-effect on PK.

The results below compare the results of dronabinol oral solution under fed conditions to Marinol capsules under fasted and fed conditions. Information on dronabinol oral solution under fasted conditions comes from Study INS-12-015.

Plasma samples were analyzed for parent drug and active metabolite using validated analytical methods.

Relative bioavailability (dronabinol oral solution vs. Marinol capsule) results under fed dosing conditions:

- Parent dronabinol (delta-9-THC): In healthy subjects, under fed dosing conditions, dronabinol oral solution (4.25 mg), demonstrated comparable AUC values to the Marinol capsule (5 mg). C_{max} following dronabinol oral solution was approximately 40% lower relative to C_{max} of Marinol capsule under fed conditions.

Relative Bioavailability summary for parent dronabinol:

Solution-fed (test) vs. Marinol fed (reference):

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
C _{max}	60.80	51.99	71.10
AUCT	88.93	79.08	100.00
AUCINF	81.93	69.04	97.24
<i>Test: Solution-fed; Reference: Marinol-fed</i>			

Clinical Pharmacology Reviewer comments:

- This was the primary comparison of interest in this study. Relative BA statistics suggest that AUC_t values were comparable for the test (solution) and reference (capsule) formulations under fed conditions. The lower 90% confidence bound for AUC_{inf} was below the 80% regulatory threshold for bioequivalence. The C_{max} for the oral solution was lower compared to Marinol under fed conditions.
- Active metabolite (11-hydroxy-delta-9-THC): Under fed conditions, the AUC values of the active metabolite for dronabinol oral solution were comparable to those from Marinol capsule, although the C_{max} was approximately 40% lower for the dronabinol oral solution.

Metabolite PK: Dronabinol solution (test) vs. Marinol capsule (reference) under fed conditions:

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
C _{max}	61.75	54.96	69.39
AUCT	85.69	80.24	91.51
AUCINF	86.16	80.96	91.70
<i>Test: Solution-fed; Reference: Marinol-fed</i>			

Clinical Pharmacology Reviewer comments:

- Despite a lower C_{max}, the metabolite AUCs were comparable to Marinol under fed dosing.

Food-effect on bioavailability:

- Parent dronabinol (delta-9-THC): a significant food-effect (fed vs. fasted exposure comparison) on the bioavailability of parent dronabinol (delta-9-THC) can be concluded for both dronabinol oral solution and Marinol capsule formulations. For the dronabinol oral solution under fed conditions, although the C_{max} values appeared to be lower by 22%, the AUC of dronabinol increased by approximately 280% (or 2.8-fold) (cross-study comparison), respectively, for the proposed product. The C_{max} and AUC values increased by 6% and 280%, respectively, for Marinol capsules under fed dosing (within-study comparison). In addition, the median T_{max} values were prolonged for approximately 4.5 hours for the dronabinol oral solution and 3.5 hours for Marinol capsules under fed conditions.

Solution-fed (test) vs. Marinol fasted (reference):

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
C _{max}	64.89	55.46	75.93
AUCT	219.14	194.82	246.50

AUCINF	236.61	201.95	277.22
<i>Test: Solution-fed; Reference: Marinol-fasted</i>			

Clinical Pharmacology Reviewer comments:

- This comparison of test solution under fed conditions to Marinol under fasted conditions again showed lower C_{max} values for dronabinol under fed dosing. AUC_T and AUC_{inf} values suggest a much higher exposure of dronabinol from the test formulation under fed conditions compared reference capsule dosed under fasted conditions. This is consistent with the marked food-effect noted for Marinol capsule as seen in the table below.

Marinol fasted vs. fed:

Parameter	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	106.73	91.36	124.69
AUCT	246.43	219.31	276.90
AUCINF	288.78	248.18	336.03
<i>Test: Marinol-fed; Reference: Marinol-fasted</i>			

Clinical Pharmacology Reviewer comments:

- A significant food-effect on dronabinol PK from Marinol capsule, with an increase in AUC_t by ~ 2.5-fold and AUC_{inf} by 2.8-fold is seen. Food did not increase dronabinol C_{max} from Marinol as the point estimate was close to 100% and the 90% confidence bounds were within the 80-125% BE bounds.
- Active metabolite (11-hydroxy-delta-9-THC): The data also suggested a food-effect on metabolite PK, with a decrease in C_{max} by approximately 33% and an increase in AUC by approximately 40% under fed conditions for Marinol capsule. For the dronabinol oral solution, a cross-study comparison suggested a decrease in C_{max} of the active metabolite by approximately 55% and an increase in AUC by approximately 19% under fed conditions.

Metabolite PK: Reference Marinol capsule fed vs. fasted:

Metabolite	Ratio (% T/R)	90 % CI LB	90 % CI UB
Cmax	67.39	60.03	75.67
AUCT	141.31	132.38	150.83
AUCINF	139.03	130.69	147.90
<i>Test: Marinol-fed; Reference: Marinol-fasted</i>			

Clinical Pharmacology Reviewer comments:

- Despite a lower C_{max} , under fed conditions, Marinol capsule showed a modest food-effect on metabolite PK, with increased AUC parameters by ~ 40 %.

QT Assessment

CDTL Comment: See Section 8 (Safety) in this review for a discussion of the QT prolonging potential of dronabinol.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Background

The sponsor is relying on the summary findings of safety and effectiveness for Marinol capsules (NDA 18651) for the indications of:

- Anorexia associated with weight loss in patients with AIDS; and
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

In addition, the sponsor performed a literature search, covering the time period from the last Marinol PI update in June 2006 to the present, to identify studies that further illustrate the utility of dronabinol for the approved indications.

- Two placebo-controlled trials and one retrospective chart review found that dronabinol increased caloric intake resulting in weight gain in AIDS/HIV patients (Bedi et al. 2010, Haney et al. 2007, DeJesus et al. 2007).
- A placebo-controlled study of dronabinol in the treatment of chemotherapy-induced nausea and vomiting (Meiri et al. 2007), and
- several reviews of recent clinical experience, have demonstrated positive effects of dronabinol on nausea intensity and vomiting rates (Slatkin 2007, Rocha et al. 2008, Cotter 2009, and Todaro 2012).

Conclusions on the Substantial Evidence of Effectiveness

The clinical reviewer concludes based on demonstration of bioequivalence of dronabinol oral solution (4.25 mg) to Marinol capsules (5 mg), the sponsor has provided evidence of effectiveness to support approval of dronabinol oral solution for the treatment of anorexia associated with weight loss in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy.

The sponsor's submitted literature publications supported the efficacy of dronabinol products for the two Marinol approved indications.

CDTL Comment: See complete clinical review by Wen-Yi Gao, MD, PhD, dated April 1, 2016 in DARRTS.

8. Safety

This section summarizes safety from the clinical review, the Controlled Substance Staff (CSS) consult review, consults reviews from the Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance (DPV) and Division of Epidemiology (DEPI), and a consult review from the QT-Intradisciplinary Review Team (QT-IRT).

Clinical Review

Summary of Data

The sponsor is relying on the summary findings of safety and effectiveness for Marinol capsules (NDA 18651) for the indications of:

- Anorexia associated with weight loss in patients with AIDS; and
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

In addition, the safety of dronabinol oral solution has been evaluated in five pharmacokinetic studies and a human abuse potential trial.

Further evaluation of the safety of dronabinol was conducted by the sponsor from postmarket sources, including reports of adverse events to AERS, to the WHO Vigibase, and in the literature.

Clinical Review

The clinical reviewer concludes dronabinol oral solution is effective for the labeled Marinol indications with an acceptable tolerability profile.

CDTL Comment: See complete clinical review by Wen-Yi Gao, MD, PhD, dated April 1, 2016 in DARRTS.

The reviewer bases this conclusion upon:

- A similar adverse event profile between dronabinol oral solution (4.25 mg) and Marinol Capsules (5 mg) in the cross-over pharmacokinetic trials. The most common adverse reactions included diarrhea, nausea, dizziness, headache and somnolence.
- Labeled gastrointestinal, psychiatric and nervous system events were no different between these formulations in the pharmacokinetic trials, and no new safety signals specific for the oral solution were identified.
- Analysis of postmarket safety reports from safety surveillance databases and the literature similarly failed to identify any new potential safety signals.

CDTL Comment: Upon review of the FAERS database and the medical literature (for the time period between February 2006 and August 2015), the DPV reviewer identified three new potential safety issues: drug interaction between dronabinol and imatinib, anaphylaxis, and severe or chronic nausea/vomiting. For additional information, see DPV consult review summarized below.

Summary of Safety in Healthy Subjects (5 Pharmacokinetic Studies and Human Abuse Liability Study)

Deaths/Other Serious Adverse Events

There were no deaths and a single non-fatal serious adverse event in the human abuse liability study (abnormal thinking that required hospitalization and was determined by the investigator to be related to a previously undiagnosed antisocial personality disorder).

Discontinuations

There were three discontinuations in Study INS 13-017 (human abuse liability study) for adverse events. In Study INS-004-15-059, one treatment emergent adverse event (TEAE) of vomiting led to treatment discontinuation (Marinol Capsule, 5 mg under fasted conditions).

Adverse events in the four pharmacokinetic studies were mostly mild and occasionally moderate in severity according to NCI-CTCAE; there was no severe event. In general, adverse events associated with dronabinol oral solution were no more common or severe than those events associated with Marinol capsules.

Non-Serious Adverse Events

The Integrated Summary of Safety (ISS) database included three dronabinol oral solution trials (INS-08-008, INS-10-012, and INS-12-015). The abuse liability study (INS-13-017) was not included, because supra-therapeutic doses were used. Study INS-06-006 was also not included, because dronabinol syrup (an early formulation) was used. The report for Study INS-004-15-059 was submitted during the review cycle.

In the ISS database, 52 subjects received 4.25 mg dronabinol oral solution, 86 received 5 mg dronabinol oral solution, and 18 subjects received 10 mg dronabinol oral solution. The comparators included 139 subjects who received 5 mg Marinol capsules, and 18 subjects who received 10 mg Marinol capsules. The most commonly involved body systems were nervous system disorders (i.e., dizziness, headache, paresthesia, somnolence), gastrointestinal disorders (nausea, abdominal pain, diarrhea), and psychiatric disorders (delusional perception, euphoric mood, anxiety, impaired concentration, clouded sensorium, insomnia).

In Study INS-004-15-059 the most commonly reported TEAEs were headache and euphoric mood.

The human abuse liability study used higher doses. No specific adverse events stand out as prominent in the human abuse study compared to the pharmacokinetic trials. Moderate anxiety was associated with dronabinol oral solution 30 mg. The remainder of adverse events were mild.

CDTL Comment: See CSS consult review summarized below. The CSS reviewer concluded there were more psychiatric adverse events (euphoric mood, thinking abnormal, and hypervigilance) in the dronabinol oral solution group compared with the Marinol group at both 10 mg and 30 mg dosages.

Laboratory parameters were evaluated for each of the pharmacokinetic studies and for the abuse liability study. No clinical significant abnormalities were identified, and no group trends were detected.

Vital signs were monitored and physical examination was conducted during each of the pharmacokinetic studies. No clinical significant abnormalities were identified, and no group trends were detected. In the abuse liability study, there were no marked changes from baseline vital sign measurements during the treatment phase and most results were within normal

limits. Four subjects showed clinically important but transient elevations of pulse rate or blood pressure.

ECG evaluations in the pharmacokinetic studies and the abuse liability study had no significant findings.

Additional Safety Issue

The clinical significance of prolonged stay of the product in oral cavity has not been studied.

Dronabinol oral solution should be swallowed instantly, because prolonged stay in oral cavity may lead to the diffusion of drug into the blood through tissues under the tongue. The pharmacokinetics differs between the administration *per os* and the sublingual. The former will go through the GI tract and the First Pass effect will only allow approximately 20% of the administered dose reaching the target sites, whereas the latter directly enters systemic blood circulation and reaching the target sites with full potency.

CDTL Comment: The Patient Information and Instructions for Use will be revised to state that after swallowing the product, the patient should drink water. This is consistent with how the product was administered in the bioequivalence study.

Controlled Substances Staff (CSS) Consult Review

This consultative review assesses the abuse potential of dronabinol oral solution and recommends appropriate scheduling of the product under the Controlled Substances Act (CSA).

Dronabinol is the generic name given to the (-) delta-9-*trans* isomer of tetrahydrocannabinol (delta-9-THC) of synthetic origin. It is considered the primary psychoactive constituent in marijuana and is currently controlled in Schedule I of the CSA.

Synthetic dronabinol in dronabinol oral solution is the same active pharmaceutical ingredient as in the RLD, Marinol capsules, and the proposed therapeutic indications are identical to those of Marinol capsules. The sponsor has requested Schedule III for their product based on their view that it is similar to Marinol capsules. However, a solution of dronabinol does not meet the criteria to be controlled under Schedule III of the CSA.

Under the CSA, a drug is placed in one of five designations called a schedule based on its “potential for abuse.” Currently, Marinol (dronabinol capsule) is categorized as Schedule III drug. At the time of its approval in 1985, Marinol was rescheduled from Schedule I to II based on its accepted medical use and high abuse potential. In 1999, it was rescheduled from Schedule II to III based on the formulation in sesame oil, which limited its abuse potential due to the difficulty in separating the active ingredient from the formulation, and its delayed onset of behavioral effects by the oral route compared to other Schedule II drugs (e.g., cocaine). Although Marinol was placed in Schedule III of the CSA, all other preparations, mixtures, compounds, and formulations of dronabinol, including cannabis, remain in Schedule I.

CSS has concluded that the dronabinol oral solution has a greater potential for abuse than Marinol capsules, and other drugs in Schedule III, and presents a higher risk of unintentional overdose, if abused. Accordingly, they recommend placing dronabinol oral solution in Schedule II of the CSA.

CDTL Comments: See the complete CSS review by Martin Rusinowitz, MD and Silvia Calderon, PhD, entered into DARRTS on February 26, 2016.

Also, nabilone (Cesamet) the other approved synthetic cannabinoid similar to delta-9-THC is Schedule II.

The following is a summary of the CSS reviewers' major conclusions:

- The product is easily manipulated for abuse by inhalation and oral routes of administration. The *in vitro* study data demonstrate that the oral solution can be 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 vaping or through other routes of abuse.
- Dronabinol oral solution 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 intentional oral abuse and presents a higher risk of unintentional overdose, especially if abused.
- Although not assessed by the sponsor, the oral solution can be readily absorbed sublingually. This raises the potential for another abuseable route of administration of high doses of dronabinol oral solution at levels that are not achievable with Marinol.
- Deficiencies were noted in the study conducted by the sponsor which evaluated the feasibility of smoking traditional cigarettes spiked with the dronabinol oral solution or with the content of Marinol capsules.
- The large content of dronabinol in the supplied dronabinol oral solution 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.
- In the human abuse potential study (Clinical Trial INS-13-017) there were more psychiatric adverse events (euphoric mood, thinking abnormal, and hypervigilance) in

the dronabinol oral solution group compared with the Marinol group at both 10 mg and 30 mg dosages.

- The human abuse potential study (INS-13-017) demonstrated 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, based upon the pre-defined primary and secondary endpoints of Drug Liking, Overall Drug Liking and Take Drug Again, as measured by a visual analog scale (VAS).

CDTL Comment: CSS requested a statistical consult for the human abuse potential study (INS-13-017). The review by Wei Liu, PhD, Division of Biometrics VI, was entered in DARRTS on January 4, 2016. The reviewer verified the sponsor's statistical tests on the primary and key secondary endpoints. The reviewer also commented that the differences between Marinol and dronabinol oral solution at either high (30 mg) or low dose (10 mg) are not statistically significant in the primary and key secondary endpoints. However, the endpoint values of dronabinol oral solution 30 mg are numerically larger than that of Marinol 30 mg. Similar observations are also seen at the dose of 10 mg, except for the endpoints "Take Drug Again" and "Overall Drug Liking." These findings have been incorporated into the CSS review.

The statistical reviewer also requested clarified wording in the Drug Abuse and Dependence section of the PI regarding the results of the study. CSS recommendations for the PI have not been finalized as of the date of this review.

Communication with the Sponsor

A teleconference was held on March 2, 2016 with the sponsor to communicate CSS's scheduling recommendation.

CDTL Comment: See information request sent to the sponsor dated March 4, 2016 in DAARTS summarizing the main points discussed during the teleconference. Meeting minutes from the teleconference were entered into DARRTS on March 10, 2016.

On March 8, 2016 the sponsor was provided some clarifying information by email in follow up to the March 7, 2016 teleconference. The sponsor was told that if they intend to submit a dispute resolution request about the scheduling determination, the request would not be a formal dispute resolution request (FDRR) per the guidance for industry, Formal Dispute Resolution: Appeals Above the Division Level, but that they may still wish to pursue a reconsideration of the CSS recommendation through informal means by contacting the CDER Ombudsman's office.

On March 10, 2016, the sponsor submitted additional information and responses to the FDA's comments of March 7, 2016, including the results of two *in vitro* abuse potential studies: a smoking-vaporizing study and an extraction study. On March 22, 2016 the sponsor was notified in a "Review Extension – Major Amendment" letter that the March 10, 2016

submission constituted a major amendment and the PDUFA goal date was extended to July 1, 2016.

After considering the totality of the clinical and *in vitro* data related to the abuse potential of SYNDROS, including the new data in the March 10, 2016 submission, CSS continues to recommend that SYNDROS be scheduled as a Schedule II upon approval.

CDTL Comment: CSS memo entered into DARRTS on April 22, 2016. See information request sent to the sponsor dated March 4, 2016 in DAARTS summarizing the main points discussed during the teleconference. Meeting minutes from the teleconference were entered into DARRTS on March 10, 2016.

As part of the March 10, 2106 submission, the sponsor responded point-by-point to the initial points raised during the March 2, 2016 teleconference by CSS. On April 25, 2016, the review team provided the sponsor with additional point-by-point CSS responses in order to facilitate a teleconference on April 26, 2016. The sponsor continues to dispute a Schedule II and requests Schedule III. During the teleconference, the review team requested that the sponsor submit for review a response containing a direct comparison between Marinol and dronabinol oral solution which addresses the following criteria (taste, ethanol content, ease of manipulation, risk of diversion, attraction to diversion, nature of high, concentration of THC, and route of administration.

CDTL Comment: Meeting minutes from the April 26, 2016 teleconference were entered into DARRTS on April 28, 2016.

At the time of this review, the sponsor has not submitted the additional information requested during the teleconference and CSS has not provided wording for Section 9 Drug Abuse and Dependence in the PI.

As noted above, CSS has recommended that dronabinol oral solution be placed in Schedule II of the CSA, though the sponsor has proposed that it be placed in Schedule III. This issue is still under review and although the overall recommendation is that the application be approved, dronabinol oral solution cannot be legally marketed until the Drug Enforcement Agency makes its determination of its scheduling.

OSE/DPV Consult Review

Background

In 2006 OSE performed a postmarketing safety review of Marinol capsules summarizing serious adverse events between approval of Marinol (May 1985) and February 9, 2006. The review recommended the Marinol PI be updated (1) with a warning about the use of the drug in elderly patients, with an emphasis on recommending a lower starting dose and (2) the risk of seizures. These risks were added to the Marinol PI in 2006.

In 2012, OSE conducted a review of the abuse, misuse, overdose and deaths associated with Marinol using FAERS data between 2006⁶ and 2012.⁷ No labeling changes were made as a result of this review.

The sponsor conducted a safety review of postmarket sources and the literature on use of dronabinol since the last update of the Marinol PI in 2006. Two literature searches were conducted by the applicant to evaluate the association between dronabinol and syncope or QT prolongation, at the request of the division.

DPV was asked to:

- review the postmarketing FAERS reports and the literature (since 2006) to evaluate whether the existing safety information on dronabinol in the proposed PI for dronabinol oral solution adequately reflects the safety profile of the drug and that no new safety signal(s) have been identified.
- provide information on risk of systemic hypersensitivity reactions (e.g., anaphylaxis) to the product.

Review Summary

The following is a summary of the reviewer's findings.

CDTL Comment: See complete DPV review by Nicholas Miles, PharmD, Division of Pharmacovigilance (DPV)-I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology dated November 19, 2015 in DARRTS.

A review of the FAERS database and the medical literature (for the time period between February 2006 and August 2015) identified three new potential safety issues: drug interaction between dronabinol and imatinib, anaphylaxis, and severe or chronic nausea/vomiting. There were two FAERS cases that reported significantly decreased imatinib levels when dronabinol was co-administered with imatinib. Regarding systemic hypersensitivity reactions, there was one case of positive rechallenge that met the Sampson clinical diagnostic criteria for anaphylaxis. Finally, there were 9 cases of nausea, vomiting, or both in this review that used dronabinol for reasons other than cancer chemotherapy induced nausea and vomiting (CINV). In these nine cases, we observed: 1) severe symptoms that are not reflected in the current label – “unable to keep any food down,” “vomiting his guts out,” and “no appetite,” and 2) severe abdominal pain, and chronic nausea and vomiting with long term dronabinol use. There was one case of a premature infant who experienced chronic nausea and vomiting with in-utero exposure to dronabinol and legalized marijuana. Although there are a small number of FAERS cases, research has shown that down-regulation and desensitization of the cannabinoid receptor type 1 (CB1) receptor in the setting of continuous delta-9-THC stimulation leads to the paradoxical effect of nausea and vomiting.

DPV-I concluded that dronabinol administration is associated with anaphylaxis and severe or chronic complaints of nausea and vomiting. In addition, FAERS cases suggest that co-administration of dronabinol and imatinib may decrease imatinib levels. Regarding nausea and vomiting, it is important for providers to be aware of the potential

⁶ Mackey, AC. Marinol (dronabinol) Postmarketing Safety Review. (Internal Report). March 2006. Reference ID: D060098.

⁷ Cao, C and Green, P. Marinol (dronabinol) and Cesamet (nabilone) Pharmacovigilance Review for Abuse, Misuse, Overdose, Accidents and Deaths. (Internal Report). December 2012. Reference ID: 3236795.

severity and chronicity of dronabinol-associated nausea and vomiting because discontinuation of the drug has resulted in resolution of symptoms. In some situations, if the association is missed, providers may increase the dronabinol dose, the offending agent, in a patient presenting with worsening nausea or vomiting.

DPV-I recommends the following for consideration:

- Update the Warnings and Precautions section of the label to include the potential risk of anaphylaxis.

CDTL Comment: The Contraindications section of the PI already states that the product is contraindicated in patients with a history of a hypersensitivity reaction to dronabinol. Specific adverse reactions attributed to hypersensitivity reactions in unconfounded postmarketing cases were added to the Contraindications section and Adverse Reactions, Post-Marketing Experience.

- Update the Warnings and Precautions section of the label to describe the potential risk of paradoxical abdominal pain, nausea, or vomiting with the following suggested language:
 - Paradoxical nausea, vomiting, or abdominal pain: During postmarketing experience, worsening of nausea, vomiting, or abdominal pain have been reported in patients treated with DRONABINOL capsules. Advise patients, their caregivers and families to notify their prescriber if the emergence or worsening of nausea, vomiting, or severe abdominal pain occur. If unexplained or clinically significant nausea, vomiting, or abdominal pain occurs, prescribers should carefully evaluate the risk and benefits of continuing treatment with DRONABINOL capsules.

CDTL Comment: A Warning and Precaution has been added to the PI regarding paradoxical nausea, vomiting and abdominal pain. See Section 12 (Labeling) of this review.

- Consult the Office of Clinical Pharmacology to evaluate the reported interaction between dronabinol and imatinib.

CDTL Comment: In an email dated March 9, 2016, the clinical pharmacology reviewer stated: We looked into the dronabinol-imatinib question during our review of drug interaction literature. We did not find publications that suggest interaction between dronabinol and imatinib. The enzyme induction potential of dronabinol is not completely understood.

Based on in vitro data from Sativex labeling, it appears that this combination product (not approved in US) which has dronabinol as one of its constituents, didn't induce CYP3A4, the principle metabolizing enzyme for imatinib. While, this may be reassuring, note also that there is no information on the enzyme induction potential of the active metabolite.

It is also possible that these patients identified by FAERS search could have been on other drugs that caused the interaction. So while we cannot rule out a potential interaction due to either the drug or its major/active metabolite, we do not have any concrete evidence to include this as a potential DDI to the dronabinol label.

- Consult the Office of Clinical Pharmacology to evaluate the potential effects of in-utero exposure.

CDTL Comment: Maternal Health team review discussed in Section 9 (Pediatrics) and also Section 12 (Labeling) of this review.

OSE/DEPI Consult Review

Background

DGIEP asked the Office of Surveillance and Epidemiology (OSE) to review post-2006 dronabinol adverse event reports and safety information in the medical literature, with special attention to high THC dose (≥ 7 mg/m²) and systemic hypersensitivity.

Review Summary

The following is a summary of the reviewer's findings.

CDTL Comment: See complete DEPI review by Joel Weissfeld, MD, MPH, Division of epidemiology I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology dated November 25, 2015 in DARRTS.

In a 2006-2015 medical literature search restricted to studies of oral THC when used to treat cancer or HIV-infected patients, DEPI found 12 articles, six available only as abstracts.¹ Four controlled and three uncontrolled studies reported adverse events for 176 and 134 patients exposed to THC, respectively. This scant information described a safety profile consistent with the Prescribing Information proposed for dronabinol oral solution. Results from one study published in 2006 cautioned against the use of dronabinol for cancer-related anorexia-cachexia syndrome. Although the study found serious adverse events imbalances, the results seem inconsistent with the larger body of evidence. Results from this one 2006 study do not constitute a new safety signal in regards to the approved dronabinol indication, nausea and vomiting from cancer chemotherapy.

Except in marijuana-experienced HIV-infected patients, the studies in this review used conventional dronabinol dosing. DEPI did not identify information about the safety of high dronabinol doses.

The twelve articles reviewed by DEPI did not identify systemic hypersensitivity or anaphylaxis as a dronabinol risk.

DGIEP may accept information in the 2006 Marinol PI as a truthful reflection of the post-2006 medical literature with respect to the safety of dronabinol used for labeled indications.

QT-IRT Consult Review

Background

Due to the time elapsed since the initial approval of Marinol and reports of syncope that have occurred in the interim, FDA requested the sponsor conduct a literature search and discussion on the QT prolonging potential of dronabinol.

In response, the sponsor submitted a published Thorough QT study (TQT) by Sellers, et al.⁸ conducted using delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) spray (Sativex), an oral mucosal spray. [REDACTED] (b) (4)

[REDACTED] (b) (4)

The TQT study evaluated the exposure-response of both THC and CBD. Upon preliminary review by the DGIEP Clinical Pharmacology team of the TQT study results, the prescribing information for Marinol, and the single-dose PK results of dronabinol oral solution from NDA 205525, it appears that the THC exposures in the TQT study cover the range of exposure expected for the dronabinol appetite stimulation indication [i.e., 2.5 to 10 mg twice daily of Marinol capsules, which is equivalent to 2.125 to 8.5 mg twice daily of dronabinol oral solution]. However, the dronabinol dosing for the antiemetic indication is higher [Marinol capsules 5 to 15 mg/m² given four to six times per day, which is equivalent to dronabinol oral solution 4.25 to 12.75 mg/m² four to six times per day].

Review Summary

Specific questions posed to the QT-IRT and their responses are shown below.

CDTL Comment: See complete QT-IRT consult review by Jiang Liu in DAARTS dated October 27, 2015.

1. Please review the study methodology and comment on whether or not the study was adequately conducted as a TQT study and whether or not you agree with Sellers, et al. conclusion that Sativex does not significantly affect ECG parameters at the doses tested (up to 36 sprays per day).

QT-IRT's response: QT-IRT never had a chance to review the study report and perform our own analysis. Based on the paper from Sellers, et al., it does not seem that THC will prolong QTc significantly. However, the TQT study has clear limitations:

1. *The studied doses are not adequate to cover the therapeutic exposure for the antiemetic indication;*
2. *The ECG assay sensitivity in this study is questionable because a typical $\Delta\Delta QTc$ timecourse for moxifloxacin was not demonstrated;*

⁸ Sellers EM, Schoedel K, Bartlett C, et al. A multiple-dose, randomized, double-blind, placebo-controlled, parallel-group QT/QTc study to evaluate the electrophysiologic effects of THC/CBD spray. *Clinical Pharmacology in Drug Development* 2013;2(3):285-94.

- Inconsistent results were presented in the paper: there are several upper bounds of the 90% CIs of $\Delta\Delta QTcI$ for THC/CBD 8-spray treatment group that were above 10 ms as shown in their figure.*

Therefore, we consider the TQT study is not adequate.

- Can the results (i.e., lack of QT effect) be extrapolated to dronabinol oral solution for the dosage regimen recommended for the indications of: (1) appetite stimulation and/or (2) nausea and vomiting?

QT-IRT's response: If the above TQT was adequate, the results would be able to be applied to dronabinol oral solution for the dosage regimen recommended for appetite stimulation. However, we consider the TQT study is not adequate especially for the antiemetic indication (see Q1).

- If the ranges of THC exposures studied by Sellers do not cover the range of doses for the antiemetic indication (which is higher than the appetite stimulation indication) would it possible for you to use the available data and model exposures to evaluate the QT effect of dronabinol at the upper limit of the antiemetic dosing range?

QT-IRT's response: We do not have the data and analysis detail to perform the extrapolation. More importantly, QT assessments based on extrapolation at a higher exposure than studied can only serve for an exploratory purpose and additional QT study will still be needed.

OSE/DPV QT Consult Review

Background

Regarding the above recommendation from the QT-IRT that a TQT study would still be required (as a Postmarketing Requirement), the review team requested a consult from OSE/DPV to search FAERS for any potential signal of QT prolongation and related adverse events with dronabinol capsules between approval (1985) and the present.

Review Summary

The following is a summary of the reviewer's findings.

CDTL Comment: See complete DPV review by Nicholas Miles, PharmD, Division of Pharmacovigilance (DPV)-I, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology dated January 12, 2016 in DARRTS.

We evaluated 83 FAERS reports of QT prolongation and related events reported in association with marijuana or dronabinol capsules. It should be noted that THC and dronabinol (a synthetic delta-9-THC) are linked in the FAERS drug product database; therefore, searching the database for dronabinol also retrieved reports for marijuana. It could not be reliably determined if the reported adverse events involved dronabinol or marijuana-derived products, which contain THC. The search terms within the SMQs that we used to query the FAERS database were extensive for capturing all potential reports of Torsades de pointes.

Overall, the majority of the reports appeared to involve patients with a history of polysubstance use disorders. These cases involved drugs that are labeled for QT prolongation and Torsades de pointes, such as methadone. Accordingly, the role of dronabinol in the reported events cannot be determined because they involved multiple medications and substances.

We are mindful of the fact that the limited reporting does not necessarily mean the absence of a signal and that FAERS data has limitations. A limitation to FAERS data includes under-reporting to the FAERS database. FDA does not receive all adverse event reports that may potentially occur with a product. Many factors can influence the reporting of an event, including the length of time a product has been marketed, and publicity surrounding an event. However, considering these factors, there does not appear to be an association between QT prolongation or Torsades de pointes and dronabinol capsules based on the data from FAERS. DPV-I will continue routine postmarketing pharmacovigilance monitoring for dronabinol capsules.

CDTL Comment: Email from Maria Walsh, ADRA in ODE III, dated February 16, 2016: For 505(b)2 applications there needs to be a scientific rationale based on the difference in dosage forms in order to require PMR/PMCs (e.g., an emerging safety issue with the drug class that would warrant a TQT study, then a study would be required of all products in the class, not just this product.

Since it cannot be concluded that the oral solution formulation of dronabinol is any more likely to prolong the QT interval than dronabinol capsules, a TQT study will not be required for this product. And, since no emerging safety issues have been identified with the cannabinoid drug class, based on the DPV review, a TQT will not be required for all cannabinoid products.

9. Advisory Committee Meeting

No advisory committee meeting was held.

10. Pediatrics

Dronabinol oral solution was discussed at a PeRC meeting on February 3, 2016.

CDTL Comment: Below is an excerpt from the final PeRC meeting minutes entered into DARRTS on February 18, 2016.

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:*
 - 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.
 - The PeRC was split on the pediatric plan for AIDS related anorexia with weight loss (see discussion above).
 - 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.

CDTL Comment: See Section 13 (Recommendations/Risk Benefit Assessment) of this review for a listing of the agreed upon pediatric PREA PMR studies.

Since the PeRC was split on a waiver versus a deferral for the study in patients 15 to 17 years of age for the AIDS-related anorexia indication, DGIEP requested a consult from OSE to perform a drug utilization search for “dronabinol” on February 9, 2016. To evaluate drug utilization by age groups (including pediatrics, the 15 to 17 age group being the most relevant) and by diagnosis for which prescriptions have been dispensed, and also by medical specialty of prescriber.

The OSE review concluded that in the outpatient retail pharmacy setting, the nationally estimated number of pediatric patients aged 15-17 years who received a dispensed prescription for dronabinol increased more than 2-fold from 261 patients in 2006 to 738 patients in 2015. The nationally estimated number of pediatric patients aged 0-14 years old also increased more than 2-fold from 420 patients in 2006 to 1,005 patients in 2015. The top prescribing specialties for dronabinol in the outpatient setting were Internal Medicine, Oncology, and Family Practice physicians.

Office based physician surveys data show that dronabinol is commonly mentioned for the treatment of Anorexia (ICD-9 code 7830) and Nausea and Vomiting (ICD-9 code 7870) in adults 18 years and older. Due to the low pediatric utilization of dronabinol in the outpatient setting, our office based physician surveys results did not capture any data associated with the use of dronabinol for anorexia among pediatric patients 15-17 years old. No diagnoses associated with the use of dronabinol were reported for pediatric patients 0-14 years old for the review period.

The review acknowledges several limitations of the data: only outpatient retail pharmacy utilization patterns were examined (non-retail and mail order/specialty pharmacies were not included). Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data.

CDTL Comment: See complete DEPI II drug utilization review by Patty Green, PharmD entered into DARRTS on March 15, 2016.

The review team, including the clinical reviewer and DPMH consultant reviewer, discussed the OSE findings and concluded that the deferral in pediatric patients 15 to 17 years of age for the AIDS-associated anorexia indication should be changed to a waiver, such that a full waiver of 0 to 17 years would be granted for this indication.

Pediatrics Consult Review

The proposed efficacy supplement triggers PREA as a new dosage form. The sponsor submitted a pediatric plan that was unchanged from the proposed waivers and studies outlined in the agreed iPSP (letter dated May 19, 2015). As noted above the pediatric plan was discussed at the PeRC meeting on February 3, 2016 and a subsequent discussion was held amongst the review team and DPMH to discuss the requirement for a clinical trial in patients 15 to 17 years of the AIDS-associated anorexia indication. DMPH agreed that this study would be extremely challenging due to the low prevalence of the condition in this population and supported a waiver for this indication.

The review also contained recommendations for the PI which were incorporated during the review cycle. See Section 12 Labeling in this review.

CDTL Comment: See complete Pediatrics Team review by Erica Radden, Division of Pediatric and Maternal Health, entered into DARRTS on April 1, 2016.

Maternal Health Consult Review

A review of the published literature was conducted for data on pregnancy or lactation or prenatal exposure to dronabinol. The reviewer concludes:

- There are no publications which could provide an estimate of the risk of spontaneous abortions or major congenital malformations in the indicated populations of pregnant women with CINV or AIDS with anorexia/weight loss or which provide data on use of dronabinol in these indicated populations.
- There is a single case report on the use of dronabinol in a pregnant woman who used the drug prior to and throughout pregnancy. The exposed infant was reportedly healthy at birth. This single publication is insufficient to assess risk of teratogenesis from dronabinol exposure.

CDTL Comment: An additional postmarketing case report of a premature infant with chronic nausea and vomiting following secondary exposure to dronabinol and legalized marijuana, identified in the DPV review, was also reviewed by the Maternal Health reviewer.

- A search of the reproductive toxicology databases found no reviews of dronabinol or Marinol in Reprotox, Shepard's or TERIS. Very limited data indicates that delta-9-THC may be transferred to the fetus during late pregnancy and the teratogenic risk is not known.
- There are multiple adverse events reported with use of dronabinol in adults including convulsions and syncope. On this basis, DPMH recommends that pregnant women should not use dronabinol during pregnancy.
- The review of dronabinol found in the LACTMED database discussed data from *Cannabis* use in lactating women, not dronabinol; however, one reference did demonstrate the presence of delta-9-THC and two of its metabolites in breast milk. The possible effects of this exposure are not known, however, there are several serious adverse events that have been reported with use of dronabinol in adults. Lactating women should not breastfeed while being treated with dronabinol.

CDTL Comment: See complete Maternal Health Team review by Carol Kasten, MD, Pediatric and Maternal Health, entered into DARRTS on April 11, 2016.

11. Other Relevant Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

Financial Disclosures

The clinical reviewer concluded the sponsor has adequately disclosed financial interests or arrangements with the clinical investigators (see Appendix 13.2). The sponsor stated that none of the clinical investigators received significant payments as defined in 21 CRG 54.2(a), (b), and (f). The sponsor reasonably disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up concerns which would possibly jeopardize the integrity of the data.

Other Good Clinical Practice (GCP) issues

The clinical reviewer concluded the sponsor has provided attestation that all the 5 studies (INS-06-006, INS-08008, INS-10-012, INS-12-015, and INS-13-017) submitted to this NDA. These studies were conducted in accordance with good clinical practice (GCP) that includes the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70). The studies were performed under IND 75,228.

DMEPA Consult Review

DMPEA was consulted on the label comprehension study and labeling for areas of vulnerability that may lead to medication errors.

Background

The proposed co-packaged oral syringe is labeled with two increments: 0.425 mL (2.125 mg) and 0.85 mL (4.25 mg), corresponding to dosing increments for the two indications. In the Dosage and Administration section of the PI, the dose is presented in both mg and mL and expressed to the hundredth or thousandth decimal place for both indications. In addition for the chemotherapy indication, the dose is calculated using the patient's body surface area (BSA); therefore, final doses must be rounded to the nearest 2.125 mg increment in order to correspond to the nearest 0.425 mL increment labeled on the oral syringe.

The following tables show the recommended dosage range by indication:

Anorexia Associated with Weight Loss in AIDS

Dose (mg)	Volume (mL)
2.125 mg	0.425 mL
4.25 mg	0.85 mL
6.375 mg	1.275 mL
8.5 mg	1.7 mL

Nausea and Vomiting Associated with Chemotherapy

Dose (mg/m²)	Volume (mL/m²)
2.125 mg/m ²	0.425 mL/m ²
4.25 mg/m ²	0.85 mL/m ²
6.375 mg/m ²	1.275 mL/m ²
8.5 mg/m ²	1.7 mL/m ²
10.625 mg/m ²	2.125 mL/m ²
12.75 mg/m ²	2.55 mL mL/m ²

There was concern amongst the review team and DMEPA that the complexity of the dosing regimen and the design of the syringe would lead to dosing errors.

CDTL Comment: See complete DMEPA consult review from Matthew Barlow, BSN, RN entered into DARRTS on March 24, 2016.

Label Comprehension Study

In the study errors occurring with the following tasks and the DMEPA reviewer concluded:

- Ability to open package
These errors would not affect the results of the study in terms of the safe and effective use of the product and no modifications to the product or labeling are needed.
- Ability to draw the solution correctly
These errors would not affect the results of the study in terms of the safe and effective use of the product and no modifications to the product or labeling are needed.

- Ability to draw the correct dosage
Four subjects drew up 0.85 mL instead of the correct 0.425 mL. Although a root cause analysis was not performed, the labeling of the oral syringe with both mg and mL units of measurement as well as the numerical similarity between certain doses (e.g., 4.25 mg and 4.25 mL) may have contributed to these errors. Additionally, the study was not designed to test subjects' ability to calculate and draw doses higher than 0.85 mL. As patients would need to calculate doses in increments of 0.425 mL or 0.85 mL due to the proposed dosing of the product and corresponding design of the oral syringe, there is concern about the risk of dosing errors since this user task was not tested.

CDTL Comment: Due to these errors observed in the study, as well as concerns for dosing errors with regard to doses above 0.85 mL and the other concerns noted above, a Discipline Review letter was sent to the sponsor on March 11, 2016. A teleconference was held on March 15, 2016 to discuss possible solutions. The sponsor agreed to revise the markings on the oral syringe to include 0.1 mL increments, to round doses in the Dosage and Administration section of the PI to the tenth decimal place, to remove the corresponding volume in mL and present only a single metric use of measure (mg and mg/m²) [e.g., 4.2 mg from 4.25 mg (0.85 mL)], and to provide a formula for the chemotherapy indication to aid health care providers in calculating and rounding doses to the nearest 0.1 mg increment. Finally, the sponsor agreed in the IFU to express the rounded dose in mL only (remove corresponding mg) and include instruction for patients on how to draw up dosages that exceed 1 mL.

The review team considers the sponsor's submission of a revised PI and IFU on March 18, 2016 to have addressed these issues.

Given the similarity with the sponsor's revised proposed oral syringe and similarity with markings on other 1 mL syringes currently on the market, DMEPA concluded another label comprehension study is not needed.

- Placement of the tip of the syringe in mouth on top of the tongue:
One study subject placed the syringe tip toward the side of the mouth. The Instructions for Use (IFU) document should improve the figure showing placement of the syringe in the mouth to avoid this error. See Section 12 Labeling
- Dispense the full dose:
The error was due to a previous task in the study and could not be assessed.

The reviewer concluded that although errors occurred in the label comprehension study, the sponsor agreed to revisions to the oral syringe to align with a standard 1 mL oral syringe, along with concurrent revisions to the Dosage and Administration section of the PI. These revisions to the design of the device should mitigate the risk of dosing errors so patients and caregivers can use the product safely and effectively.

CDTL Comment: Additional DMEPA comments on the proposed syringe label, carton labeling, and IFU were also provided and communicated to the sponsor. See Section 12 Labeling of this review.

Proprietary Name Consult

On July 17, 2015 the sponsor submitted “Syndros” as proposed proprietary name (previously submitted September 19, 2014, before refuse to file).

The proposed proprietary name, Syndros was found to be conditionally acceptable.

CDTL Comment: See correspondence to sponsor from DMEPA in DARRTS dated October 13, 2015.

Request for Inspection of Biopharmaceutical Site

Study Number INS-12-015

Study Title A Single-Dose, Replicate Crossover Design Comparative Bioavailability Study of Dronabinol Oral Solution 4.25 mg versus Marinol® Capsules 5 mg under Fasted Conditions

Clinical Site

Worldwide Clinical

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Analytical Site

(b) (4)

On August 4, 2015, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection of the clinical or analytical sites, as OSIS recently inspected the sites and the inspectional outcome from the inspections was classified as No Action Indicated (NAI).

See OSIS/DNDBE memorandum in DARRTS from Shila NKah dated August 4, 2015.

12. Labeling

Prescribing Information

Below is a summary of the substantive issues discussed during the review. Comments from the review team and consultants (e.g., DMEPA, Maternal Health, and Pediatrics) have been incorporated. However, at the time of this review, the PI is not considered to be substantially complete and the sections noted below are still pending.

OPDP did not have any comments on the PI.

CDTL Comment: See OPDP review by Meeta Patel, PharmD entered in DARRTS February 11, 2016.

HIGHLIGHTS

In general, revisions to this section were made in alignment with the revisions in the Full Prescribing Information and will not be described here.

The Product Title line notes that the CSA Scheduling determination is pending approval by the DEA, i.e., C-X. The X will be removed at the time the determination is made and the sponsor will submit a labeling supplement post-approval to remove the X designation.

SYNDROS (dronabinol) solution, C-X

The Established Pharmacologic Class is “cannabinoid”.

1 INDICATIONS AND USAGE

The same wording of the indications, as in the Marinol PI, is used with the addition of “Acquired Immune Deficiency Syndrome” to define AIDS, when used for the first time in labeling.

SYNDROS is indicated in adults for the treatment of:

- anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS); and
- nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

2 DOSAGE AND ADMINISTRATION

Important Administration Instructions



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

Other Labeling

Proprietary Name Consult

On July 17, 105 the sponsor submitted “Syndros” as proposed proprietary name (previously submitted September 19, 2014, before refuse to file).

The proposed proprietary name, Syndros was found to be conditionally acceptable.

CDTL Comment: See correspondence to sponsor from DMEPA in DARRTS dated October 13, 2015.

Patient Labeling (i.e., Patient Information and Instructions for Use)

Patient Information

At the time of this review, the PI is not considered to be substantially complete. Therefore, DMPP has not completed their review of the Patient Information and comments are pending.

Instructions for Use (IFU)

Comments from the review team and DMEPA on the IFU were sent to the sponsor in the Discipline Review letter on March 11, 2016 and the sponsor addressed the comments.

Of note, a step was added to the IFU to instruct the patient/caregiver to immediately follow oral administration of the product with a drink of water. This instruction is consistent with the conduct of the pivotal bioequivalence study (INS-12-015) and was added to mitigate the potential for sublingual drug absorption.

At the time of this review, DMPP has not completed their review of the IFU and comments are pending.

Carton and Container Labeling

Comments from DMEPA and OPQ were sent to the sponsor in the Discipline Review letter on March 11, 2016. There were no OPDP comments on the carton/container labeling. Final carton and container labeling are pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The review team, with the exception of OPQ, recommends approval of dronabinol oral solution for the treatment of:

- Anorexia associated with weight loss in patients with AIDS (acquired immune deficiency syndrome);
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

The OPQ deficiencies apply only to the labeling of the product, not the identity, strength, purity or quality of the drug product.

Risk Benefit Assessment

Bioequivalence under fasted conditions was demonstrated for dronabinol oral solution (4.25 mg) and dronabinol (Marinol) capsules (5 mg). Therefore, the sponsor may rely on the summary findings of safety and safety and effectiveness for Marinol capsules (NDA 18651) for the indications of:

- Anorexia associated with weight loss in patients with AIDS;
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Bioequivalence criteria were not met for the active metabolite (11-hydroxy-delta-9-TCH) in dronabinol oral solution under fasted conditions (lower exposure compared to Marinol capsules), but it is not a regulatory requirement to meet the criteria for the metabolite and the clinical significance is minimized by the fact that the drug is titrated to effect for both indications.

Under fed conditions, the parent dronabinol and active metabolite AUC's were comparable between the two formulations, while the C_{max} for the parent and metabolite was approximately 40% lower with the oral solution compared to Marinol capsules.

When comparing fed vs. fasted conditions, there was found to be a significant effect of food on the bioavailability of parent dronabinol and the active metabolite of both the oral solution and Marinol capsules, i.e., lower C_{max} , increased AUC, and increased time to C_{max} (i.e., T_{max}). This information is useful to inform dosing recommendations with regards to food in the product labeling.

A similar adverse event profile was observed between a single dose of dronabinol oral solution (4.25 mg) and Marinol capsules (5 mg) in human subjects. The most common adverse reactions included diarrhea, nausea, dizziness, headache and somnolence, and were consistent with the known effects of dronabinol. In the human abuse potential study there were more psychiatric adverse events (euphoric mood, thinking abnormal, and hypervigilance) in the dronabinol oral solution group compared with the Marinol group at single supratherapeutic doses (both 10 mg and 30 mg).

The human abuse potential study demonstrated 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. However, the CSS review team concluded that dronabinol oral solution, by the nature of the formulation (sweetened 50% w/w alcoholic solution to-be-marketed in a 30 mL bottle), is more easily manipulated for abuse and presents a higher risk of overdose. Therefore, the CSS recommendation is to place dronabinol oral solution in Schedule II of the CSA. Labeling of the product will also convey the risk of abuse and provide management recommendations in the case of overdosage.

Analysis of postmarket safety reports from safety surveillance databases and the literature identified one new potential safety issue that is not currently labeled for Marinol: paradoxical nausea, vomiting or abdominal pain, similar to cannabinoid hyperemesis syndrome, when used long-term. A warning will be added to the labeling for the product to alert prescriber to consider dose reduction or discontinuation if a patient develops new or worsening symptoms while taking the drug.

Dronabinol oral solution (5 mg/mL) contains (b)(4)% w/w dehydrated alcohol and (b)(4)% w/w propylene glycol. The labeling will also convey risks associated with the presence of these excipients: a contraindication against use within 14 days of disulfiram or metronidazole due to the risk of a disulfiram-like reaction (characterized by abdominal cramps, nausea, vomiting, headaches and flushing), a warning about possible toxicity in preterm neonates mediated by a diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse reactions including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and electrocardiogram (ECG) changes, and hemolysis.

Due to reports of syncope that have occurred in the interim, FDA requested the sponsor address the QT prolonging potential of dronabinol in the October 14, 2014 RTF letter (not a deficiency). A published study submitted by the sponsor using a similar delta-9-THC combination product with cannabidiol in the form of an oral mucosal spray, was not found to be an adequate TQT study by the QT-IRT. Available nonclinical data, also submitted by the sponsor, did not provide useful information for evaluating the potential of delta-9-THC to affect ventricular repolarization. ECG evaluations in the pharmacokinetic studies and the abuse liability study had no significant findings. A postmarketing review (1985 to 2015) concluded there did not appear to be an association between QT prolongation or Torsades de pointes and dronabinol capsules. Since no emerging safety signal was identified and it cannot be concluded that the oral solution formulation of dronabinol is any more likely to prolong the QT interval than dronabinol capsules, a TQT study will not be required of the sponsor.

Dronabinol oral solution is to-be-marketed in a clear, amber-colored glass bottle with a fill volume of 30 mL containing 150 mg drug (5 mg/mL). The solution is co-packaged with a press-in bottle adapter and an oral dispenser (syringe). As such, it is considered a combination drug/device product. The identity, strength, purity or quality of the drug product was found to be acceptable. It was concluded there is reasonable assurance of safety for the estimated maximum daily intake of the excipients and for the proposed impurity limits in the drug

substance and drug product. The oral dispenser and press-in bottle adapter were found to accurately dispense the product, to be compatible and function as intended, and there was no identified safety concern for exposure to potential leachables/extractables.

The sponsor's iPSP has been previously agreed upon and addresses the RTF letter of October 10, 2014. Under Pediatric Research Equity Act (PREA) the sponsor has committed to conduct the following studies as Postmarketing Requirements: nonclinical toxicity studies in neonatal rats to inform pharmacokinetic and clinical studies in pediatric cancer patients who failed to respond adequately to conventional antiemetic treatments from birth to 17 years of age and pediatric patients with acquired immune deficiency syndrome (AIDS) aged 15 years to 17 years. During the review cycle, the team decided not to require the clinical study in patients 15 to 17 years of age for the AIDS-associated anorexia indication and instead to issue a full waiver for patients 0 to 17 years of age for this indication.

In summary, the benefit of dronabinol oral solution outweighs the identified risks, which can be addressed through labeling and CSA scheduling. As noted above, the CSS has recommended that dronabinol oral solution be placed in Schedule II of the CSA, though the sponsor has proposed that it be placed in Schedule III. This issue is still under review.

The overall recommendation is that dronabinol oral solution can be approved, although it cannot be legally marketed until the Drug Enforcement Agency makes its determination on its scheduling. In addition, finalization of product labeling (Prescribing Information, Patient Information, Instructions for Use, and carton/container) remains ongoing at the time of this review.

Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following are the agreed upon Pediatric Research Equity Act (PREA) Postmarketing Requirements:

1. Twenty-eight day, daily, repeat dose, oral gavage dose-range finding toxicity study in neonatal rats to determine dronabinol oral solution doses to inform study PMR 2.

Scheduled Milestones:

Study Completion:	06/2016
Final Report Submission:	01/2017

2. Three-month repeat dose toxicity and toxicokinetic study in neonatal rats with a 28-day recovery period.

Scheduled Milestones:

Final Protocol Submission:	01/2017
Study Completion:	11/2017
Final Report Submission:	06/2018

3. Deferred study under PREA to evaluate the pharmacokinetics of dronabinol oral solution for the treatment of chemotherapy induced nausea and vomiting (CINV) in pediatric cancer patients who failed to respond adequately to conventional antiemetic treatments from birth to 17 years of age.

Scheduled Milestones:	Final Protocol Submission:	09/2018
	Study Completion:	09/2020
	Final Report Submission:	02/2021

4. Deferred pediatric study under PREA to evaluate the tolerability and efficacy of dronabinol oral solution for the treatment of chemotherapy induced nausea and vomiting (CINV) in pediatric patients who failed to respond adequately to conventional antiemetic treatments aged birth to 17 years.

Scheduled Milestones:	Final Protocol Submission:	06/2021
	Study Completion:	06/2023
	Final Report Submission:	12/2023

5. Recommended Comments to the Applicant

Not applicable.

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/s/

JOETTE M MEYER
05/20/2016