CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205525Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 205525
Product Name: Dronabinol oral solution

PMR/PMC Description: 3044-1
Twenty-eight day, daily, repeat dose, oral gavage dose-range finding toxicity study in neonatal rats to provide rationale for dose selection for the 3 month neonatal rat toxicity study with Syndros (dronabinol oral solution).

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	08/2016
	Study/Trial Completion:	11/2016
	Final Report Submission:	01/2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This study is needed to inform dose selection in the pivotal 3-month oral toxicity study of dronabinol in neonatal rats, which is required to support the initiation of pediatric trials for all age groups. The Agency has agreed to allow the pediatric development program to begin after approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3953715

This study will serve as the basis of dose selection for the pivotal 3-month oral toxicity study of dronabinol in neonatal rats.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 28-day oral dose-ranging toxicity study of dronabinol in neonatal rats.

Reference ID: 3953715

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other
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_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3953715

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3953715

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 205525
Product Name: Dronabinol oral solution

PMR/PMC Description: 3044-2
Three-month repeat dose toxicity and toxicokinetic study in neonatal rats with a 28-day recovery period to provide safety assessment of Syndros (dronabinol oral solution) for pediatric clinical studies

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	01/2017
	Study/Trial Completion:	11/2017
	Final Report Submission:	06/2018
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The Agency has agreed to allow the pediatric development program to begin after approval. This study is required to support the initiation of pediatric trials for all age groups.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3953715

The study is needed to provide assurance of safety and inform the risk assessment for pediatric patients in clinical trials. The data from this study will be used for determining the maximum acceptable levels of systemic exposure to dronabinol in pediatric patients. The Sponsor's draft protocol includes a [redacted] (b) (4), which will be of major importance in supporting the objectives of this study given the [redacted] (b) (4).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☒ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Reference ID: 3953715

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other
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_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3953715

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3953715

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205525
Product Name: dronabinol oral solution

PMR/PMC Description: 3044-3
Deferred [redacted] (b) (4) under PREA to evaluate the pharmacokinetics of Syndros (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. [redacted] (b) (4)

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/2018
Trial Completion:	11/2021
Final Report Submission:	05/2022
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA PMR agreed upon during this review cycle. Under the regulations in place at the time of this NDA submission, an agreed iPSP was in place prior to NDA resubmission. Adult studies are completed and ready for approval, and nonclinical juvenile toxicity data need to be conducted to support initiation of pediatric clinical trials in children <17 years old.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3953715

This is a PREA PMR study to evaluate the PK of dronabinol oral solution in pediatric patients aged 0 to less than 17 years old.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4) in pediatric chemotherapy induced nausea and vomiting (CINV) patients will be performed in children 0 to 17 years of age who have cancer and are undergoing treatment.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

Reference ID: 3953715

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3953715

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205525
Product Name: dronabinol oral solution

PMR/PMC Description: 3044-4
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.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	07/2022
	Study/Trial Completion:	09/2025
	Final Report Submission:	03/2026
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA PMR agreed upon during this review cycle. Under the regulations in place at the time of this NDA submission, an agreed iPSP was in place prior to NDA resubmission. Adult studies are completed and ready for approval, and nonclinical juvenile toxicity data need to be conducted to support initiation of pediatric clinical trials in children <17 years old.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This is a PREA PMR study to evaluate the efficacy and safety of dronabinol oral solution in pediatric patients aged 0 to less than 17 years olds receiving (b) (4) emetogenic chemotherapy.

Reference ID: 3953715

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a pivotal [redacted (b) (4)] tolerability and efficacy study in pediatric cancer patients age 0-17 years old receiving [redacted (b) (4)] emetogenic chemotherapy. The primary endpoint will be [redacted (b) (4)]

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Reference ID: 3953715

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3953715

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 205525
Product Name: Dronabinol oral solution

PMR/PMC Description: 3044-5
Pre-/postnatal developmental toxicology study in rats exposed to Syndros (dronabinol oral solution) to assess the risk of neurotoxicity.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/2016
	Study/Trial Completion:	10/2017
	Final Report Submission:	07/2018
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Recent publications indicate a potential for neurocognitive impairment following prenatal exposure to delta-9-THC (dronabinol). Although the label for the reference product (Marinol) does not indicate that postnatal developmental effects were observed, it is likely that the pre-/postnatal developmental study that supported approval of Marinol used methods that were inadequate for assessing neurocognitive impairment or other subtle signs of developmental neurotoxicity.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3953715

This study is needed to provide adequate information about the risk of developmental neurotoxicity following prenatal exposure to dronabinol. The study results should be included in subsection 8.1 (Pregnancy) of the labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pre-/postnatal developmental toxicology study in rats

Reference ID: 3953715

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Pre-/postnatal developmental toxicology study in rats

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3953715

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3953715

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/s/

MAUREEN D DEWEY
06/30/2016

ANDREW E MULBERG
07/01/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Addendum

Date: June 29, 2016

From: Carol H. Kasten, MD, Medical Officer
Maternal Health Team, Division of Pediatric and Maternal Health
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Team Leader
Maternal Health Team
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Gastroenterology and Inborn Errors Products

Drug: Syndros (dronabinol) oral solution, NDA 205-525, IND 75-228

Sponsor: Insys Therapeutics, Inc.

Indication: SYNDROS is a cannabinoid indicated in adults for treatment 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.

Subject: Addendum to prior consult

Reference ID: 3952738

PURPOSE

This Memo revises the labeling language first recommended for the Syndros (dronabinol)[1] application in the DPMH review dated April 6, 2016.[2]

BACKGROUND

DPMH was consulted by the Division of Gastroenterology and Inborn Errors (DGIEP) to provide recommendations for Syndros labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule (PLLR). The DPMH Review of April 6, 2016 is associated with the original application for which action is pending. This Memo revises prior labeling recommendations for Syndros in the Pregnancy subsection based on two issues:

- The alcohol content of the Syndros formulation and the risk of fetal harm
- The nonclinical data in the Syndros labeling for prenatal THC exposure and potential risk of neurotoxicity

DISCUSSION

Alcohol Content of Syndros Formulation

The reader is referred to the Pharmacology Toxicology Review, Primary Author Fang Cai, PhD, for a complete discussion of the alcohol content in Syndros.[3] THC is immiscible in water and the applicant selected dehydrated alcohol as one of the solvents for Syndros liquid. The maximum recommended daily dose (MRDD) of Syndros would contain (b) (4) mL/day of alcohol for a 60 kg patient. Alcohol is toxic to the fetus at all stages of development and should not be consumed during pregnancy.[4] The labeling has been revised accordingly.

Nonclinical Data Demonstrating Neurotoxicity of Prenatal Exposure to THC

The Syndros NDA utilized the 505(b)(2) pathway using Marinol (NDA 18-651) as the Reference Listed Drug (RLD) for approval. Marinol was approved on May 31, 1985 and the sponsor relied on Marinol animal data (b) (4). However, since approval of Marinol, nonclinical publications studying the effects of THC on rodent neuro-development have demonstrated that the endocannabinoid system is present in early stages of embryonic and fetal development[5] and that prenatal THC exposure is associated with on rodent neuro-developmental toxicities.[6,7,8] Persistent damage to

[1] The active pharmaceutical ingredient in Syndros liquid is dronabinol, a cannabinoid that is a synthetic form of the principal psychoactive compound in *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC).

[2] DPMH-MHT Review Syndros (dronabinol) NDA 205-525, dated April 6, 2016, Carol H. Kasten, MD, Primary Author. DARRTS Reference ID 3913498

[3] Pharmacology Toxicology NDA Review and Evaluation, Fang Cai, PhD, David Joseph, PhD authors. DARRTS Reference ID: 3890644.

[4] Department of Health and Human Services. U.S. Surgeon General Releases Advisory on Alcohol Use in Pregnancy; urges women who are pregnant or who may become pregnant to abstain from alcohol(http://www.cdc.gov/ncbddd/fasd/documents/surgeongenbookmark.pdf) Washington, DC; 2005. Accessed June 21, 2016,

[5] Schneider M. Cannabis use in pregnancy and early life and its consequences: animal models. Eur Arch Psychiatry Clin Neurosci 2009;259:383–393.

[6] Lindsay S, Zhao N, *et al.* Prenatal tetrahydrocannabinol (THC) alters cognitive function and amphetamine response from weaning to adulthood in the rat. Neurotoxicol Teratol 2012;34:63–71.

[7] Campolongo P, Trezza V, *et al.* Developmental consequences of perinatal cannabis exposure: behavioral and neuroendocrine effects in adult rodents. Psychopharmacol 2011; 214:5–15.

[8] See Schneider.

Reference ID: 3952738

learning, memory and attention have been reported following prenatal THC exposure as has a reduction in fetal growth.[9] Some studies in the children of women who used cannabis during pregnancy have demonstrated similar findings; however, these findings have not been consistent.[10,11] Findings in animals have raised concern regarding the potential effects of prenatal exposure to THC in humans. Further review of nonclinical data may require revisions to labeling for Syndros and other THC-containing drugs. DPMH has revised the language in (8.1) Pregnancy to reflect the potential risks of prenatal use Syndros.

CONCLUSION
Final labeling will be negotiated with the Applicant and may not fully reflect changes recommended here.

The following are the DPMH-MHT recommendations for the proposed labeling for dronabinol in PLLR format.

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

HIGHLIGHTS

——USE IN SPECIFIC POPULATIONS——

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise HIV infected women not to breastfeed and women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for 9 days after the last dose (8.2)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

[9] See Lindsay.
[10] Zuckerman B, Frank D, *et al*. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320:762–768.
[11] Gunn J, Rosales C, *et al.* Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 2016;6:e009986.

Reference ID: 3952738

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SYNDROS, a synthetic cannabinoid containing alcohol, may cause fetal harm. Avoid use of SYNDROS in pregnant women. Although there is little published data on the use of synthetic cannabinoids during pregnancy, use of cannabis (e.g., marijuana) and use of alcohol during pregnancy have been associated with adverse fetal/neonatal outcomes *[see Clinical Considerations]*. Cannabinoids have been found in the umbilical cord blood from pregnant women who smoke cannabis. In animal reproduction studies, no teratogenicity was reported in mice administered dronabinol at up to 30 times the MRHD (maximum recommended human doses) and up to 5 times the MRHD for patients with AIDS and cancer, respectively. Similar findings were reported in pregnant rats administered dronabinol at up to 5 to 20 times the MRHD and 3 times the MRHD for patients with AIDS and cancer, respectively. Decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions were observed in both species at doses which induced maternal toxicity. In published studies, offspring of pregnant rats administered delta-9-THC during and after organogenesis have been reported to exhibit neurotoxicity with adverse effects on brain development, including abnormal neuronal connectivity and impairments in cognitive and motor function *[see Data]*.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Published studies suggest that during pregnancy, the use of cannabis, which includes THC, whether for recreational or medicinal purposes, may increase the risk of adverse fetal/neonatal outcomes including fetal growth restriction, low birth weight, preterm birth, small-for-gestational age, admission to the NICU, and stillbirth. Therefore, use of cannabis during pregnancy should be avoided.

SYNDROS contains alcohol. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development. Avoid use of SYNDROS in pregnant women.

Data

Human Data

Delta-9-THC has been measured in the cord blood of some infants whose mothers reported prenatal use of cannabis, suggesting that dronabinol may cross the placenta to the fetus during pregnancy. The effects of delta-9-THC on the fetus are not known.

Animal Data

The recommended dose ranges for SYNDROS in AIDS and cancer patients are designed to achieve the same systemic exposure ranges as with the recommended dose ranges for dronabinol capsules. Therefore, animal to human dose multiples, as shown below, are based on the MRHDs (maximum recommended human doses) for dronabinol capsules, instead of the MRHDs for SYNDROS, which are 15% lower. This approach for dose comparison between animals and humans is supported by the demonstrated difference in dronabinol bioavailability between SYNDROS and dronabinol capsules.

Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m^2, equivalent to 1 to 30 times the MRHD of 15 mg/m^2/day (dronabinol capsules) in AIDS patients or 0.2 to 5 times the MRHD of 90 mg/m^2/day (dronabinol capsules) in cancer patients, and in rats at 74 to 295 mg/m^2 (equivalent to 5 to 20 times the MRHD of 15 mg/m^2/day in AIDS patients or 0.8 to 3 times the MRHD of 90 mg/m^2 in cancer patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses that produced less maternal toxicity.

Review of published literature indicates that the endocannabinoid system plays a role in neurodevelopmental processes such as neurogenesis, migration, and synaptogenesis. Exposure of pregnant rats to delta-9-THC (during and after organogenesis) may modulate these processes to result in abnormal patterns of neuronal connectivity and subsequent cognitive impairments in the offspring. Nonclinical toxicity studies in pregnant rats and newborn pups have shown prenatal exposure to THC which resulted in impairment of motor function, alteration in synaptic activity, and interference in cortical projection of neuron development in the offspring. Prenatal exposure has shown effects on cognitive function such as learning, short- and long-term memory, attention, decreased ability to remember task, and ability to discriminate between novel and same objects. Overall, prenatal exposure to THC has resulted in significant and long-term changes in brain development, cognition, and behavior in rat offspring.

8.2 Lactation

For mothers infected with the Human Immunodeficiency Virus (HIV), the Centers for Disease Control and Prevention recommend not to breastfeed their infants to avoid risking postnatal transmission of HIV. Because of the potential for HIV transmission in breastfed infants, advise women infected with HIV not to breastfeed while taking SYNDROS.

For mothers with nausea and vomiting associated with cancer chemotherapy, there are limited data on the presence of dronabinol in human milk, the effects on the breastfed infant, or the effects on milk production. The reported effects of inhaled cannabis transferred to the breastfeeding infant have been inconsistent and insufficient to establish causality. Because of the possible adverse effects from SYNDROS on the breastfeeding infant, advise women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for 9 days after the final dose.

17 PATIENT COUNSELING INFORMATION

Pregnancy *[see Use in Specific Populations (8.1)]*

- Advise a pregnant woman of the potential risk to a fetus and to avoid use of SYNDROS during pregnancy.

Lactation *[see Use in Specific Populations (8.2)]*

- Advise HIV infected women with anorexia associated with weight loss, not to breastfeed. Advise women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for 9 days after the last dose.

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/s/

CAROL H KASTEN
06/29/2016

TAMARA N JOHNSON
06/29/2016

LYNNE P YAO
06/30/2016

M E M O R A N D U M

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

Date: June 28, 2016

To: Douglas C. Throckmorton, MD
Deputy Center Director for Regulatory Programs
Center for Drug Evaluation and Research

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Silvia N. Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 205-525 for Dronabinol Oral Solution (Oral solution: 150 mg/30 mL, or 4.25 mg/0.85mL delivered dose) Scheduling Recommendation Dispute Resolution

Materials Reviewed: DARRTS, NDA 205-525: SYNDROS (Dronabinol Oral Solution), Sequence No. 0023: Response to Information Request, 3/10/2016, Sequence No. 0027: Information Amendment: Additional Abuse Potential Study

I. SUMMARY

1. Background

Upon review of all data related to the abuse of the Dronabinol Oral Solution (SYNDROS) provided by the Sponsor under the NDA 205-525, the Controlled Substance Staff (CSS) determined that SYNDROS should be rescheduled from Schedule I to Schedule II of the Controlled Substances Act (CSA), upon FDA approval. CSS review can be found in DARRTS, NDA 205525, Calderon, Silvia N., 2/26/16.

On March 2, 2016, the CSS Team and members of the Division of Gastroenterology and Inborn Errors Products (DGIEP) contacted the Sponsor via telecom to convey CSS's findings and recommendation for scheduling. The Sponsor was also informed about their recourse to dispute CSS's findings. A list of technical findings discussed on the telecom was sent to the Sponsor on March 4, 2016. The Sponsor

responded to these technical points on March 10, 2016 (DARRTS, NDA 205-525, Sequence 0023, 3/10/2016). CSS review can be found in DARRTS, NDA 205-525, Calderon, Silvia N., 4/22/16.

The current memorandum responds to the Sponsor's assessment of the abuse potential of SYNDROS and takes under consideration new information submitted by the Sponsor on May 25, 2016, as a follow-up to the telecom held between the FDA and the Sponsor on April 26, 2016. This submission includes a study report of a Consumer Preference Study designed to assess the taste and preference of SYNDROS and Marinol capsules among recreational marijuana users, and a discussion of the general properties of the formulation the Sponsor believes contribute to the abuse potential of SYNDROS. These properties include the pharmacokinetic profile of the formulation, dronabinol's psychoactive effects, considerable abuse of marijuana relative to Marinol capsules, data from human abuse potential studies as well as data from in vitro manipulation studies. CSS has reviewed all aspects of the abuse potential of SYNDROS discussed by the Sponsor in this new submission, including the newly submitted Consumer Preference Study (Comparing the Taste of Dronabinol Solution Placebo to Dronabinol Capsule Placebo Study: INS004-16-080). A brief description of this study follows.

- *Consumer Preference Study Description*

In response to FDA's comments at the telecom held on May 25, 2016, the Sponsor conducted a Consumer Preference Study with the objective of evaluating the taste and preference of SYNDROS and Marinol among recreational marijuana users.

Twenty-seven subjects (21 males and 6 females), aged 21 to 45 years old, who met inclusion and exclusion criteria completed the study. As per inclusion criteria addressing cannabinoid and alcohol use, subjects had to have smoked marijuana or hashish, or have taken oral THC at least once a week for the past three months, had to have smoked marijuana or hashish, or taken oral THC at least four times in one week in the past three months, and had to use marijuana or hashish with alcohol at times. Twenty-one subjects (78%) reported to be "familiar with a prescription drug called Marinol", whereas six subjects (22%) claimed not to be familiar with Marinol.

Subjects were asked to consume 30 mL of placebo oral solution and alternatively 17 Dronabinol placebo capsules. Subjects responded to questions about taste, about their favorite alcoholic drink, and were asked to compare the taste of the solution to their favorite drink. For capsules, the subjects were asked to report how hard it was to swallow the capsules and to rate the taste of the capsules. Subjects also commented on their experience taking both placebo formulations.

Subjects were also asked how much they would be willing to pay for a bottle of liquid "Marinol", that contained the amount consumed in the study or for a bottle of Marinol capsules that contains 60 capsules.

In addition, subjects were asked to rate both formulations as a substitute for their preferred marijuana, which product would they more likely use to get high, and the likelihood of taking either formulation without a prescription.

CONCLUSIONS

This section summarizes the key findings of the Consumer Preference Report submitted by the Sponsor under the May 25, 2016 amendment. All the other data relevant to the abuse of SYNDROS was reviewed and discussed in prior reviews from CSS (DARRTS, NDA 205525, Calderon, Silvia N., 2/26/16 and 4/22/16).

1. **The Consumer Preference Study results do not affect CSS's prior findings that the pattern of abuse of SYNDROS may be different to that of Marinol capsules due to formulation differences.**

2. **Although, at the telecom held between the FDA and the Sponsor on April 26, 2016, the Sponsor stated that they were not going to conduct new studies, the Sponsor proceeded with the Consumer Preference Study. The Sponsor did not submit a proposed study protocol or statistical analysis to FDA for review prior initiation of the study.**

3. **The Consumer Study Report indicates that study participants:**

   a. **Find the alcoholic taste of SYNDROS unattractive; however, this was not characterized as a potential deterrent to or diminution of abuse. Some of the subjects stated that SYNDROS tasted like vodka, or that it needed some kind of flavor to be more palatable. Subject liking of the taste of alcohol and experience in drinking alcohol were not considered as inclusion criteria in subject recruitment.**

   b. **Display a stronger preference for smokable marijuana. This outcome was expected considering the subjects were selected based on their marijuana smoking patterns, and not on their oral consumption of marijuana products or their alcohol drinking experience. This finding is irrelevant when comparing the abuse potential of SYNDROS to that of Marinol.**

      Subjects were included in the study based on their smoking marijuana behavior OR oral THC intake. Responses were not analyzed taking under consideration the history of cannabinoid use of the enrolled subjects. Subjects' comments include statements such as the dose of the liquid seemed to "be a bit much", willingness to take the solution with lemonade, liking the oral consumption of THC either in the solution form or capsules to avoid smoking, liking the act of smoking, dislike for both oral formulations.

   c. **Would be willing to pay more for Marinol capsules than for SYNDROS. The question about how much the subjects were willing to pay for one formulation over the other was biased towards the resulting outcome, since the comparison was based on the subject's willingness to pay for 30 mL of SYNDROS or 60 capsules of**

Marinol. Subjects were told at the beginning of the study that the amount of THC contained in SYNDROS was equivalent to the amount of THC contained in 17 Marinol capsules.

d. Were able to ingest 17 Marinol capsules as easily as drinking the 30 mL of SYNDROS. However, as indicated by the Sponsor, subjects may have preferred to use the capsules because of their ability to control the amount ingested. This observation reinforces the concept that individuals abusing SYNDROS may not be aware of the amount of THC ingested when drinking the solution.

2- The Sponsor claims that the cost of SYNDROS, which is estimated to be between $(b) (4) and $(b) (4), will discourage the abuse or misuse of the formulation. Although this is speculative, the price or street value of a controlled substance is not one of the factors that the Agency typically weighs in the overall assessment of the abuse potential of a substance or drug.

3- The remaining issues presented in the Sponsor's submission are adequately refuted in prior CSS reviews :

a. SYNDROS and Marinol capsules have the same pharmacology and similar pharmacokinetics. However, these formulations differ in their chemical and physical properties. Formulation differences may account for a different abuse potential because the formulation may have a direct effect on the route of abuse enabling the subject to convert the drug to their individual preferred route of abuse, the population abusing the product, and patterns of abuse and expected adverse effects associated with the ways the product is abused.

b. SYNDROS can be easily abused orally without any manipulation of the formulation and through the inhalation route upon manipulation of the formulation. Similarly, delta-9-THC-containing products in the form of edibles and drinks are typically abused orally.

c. The emerging pattern of oral abuse of delta-9-THC containing products, in the form of marijuana edibles or drinks, is of concern. Oral ingestion of delta-9-THC is associated with a higher risk of overdose and occurrence of psychiatric adverse events, including but not limited to psychosis, hallucinations, depersonalization, mood alterations, and paranoia.

d. Several cases of delta-9-THC unintentional overdoses from eating delta-9-THC-containing products were reported in the peer review literature. These cases required hospitalization and treatment, and in one case death of the individual resulted. (Chaudry, Moss, Bashir, & Suliman, 1991; Hancock-Allen, Barker, VanDyke, & Holmes, 2015; Hudak, Severn, & Nordstrom, 2015; Mehrpour, Karrari, & Afshari, 2012; Nicks, 2014; Sapienza, 2006; Weiss, 2015).

e. In vitro evaporation studies (drying studies) showed that the alcoholic component of SYNDROS is readily volatilized when exposed to minimal heat, affording concentrates that could be used for smoking or vaping.

f. Data from the extraction studies conducted by the Sponsor shows that dronabinol can be more efficiently extracted from SYNDROS than from Marinol capsules.

g. In vitro data predict that manipulation of SYNDROS for obtaining samples for smoking or vaporization is feasible and more efficient that when using Marinol capsules. In vitro data also shows that more than 20% of the Marinol sample is lost in the manipulation process.

h. When conducting vaporization studies using the Volcano vaporizer, under the limited conditions studied by the Sponsor, dronabinol is recovered from SYNDROS and not from Marinol.

i. When conducting vaporization studies using the e-cigarette selected by the Sponsor and under the non-validated conditions used by the Sponsor, low levels of dronabinol are recovered from non-manipulated SYNDROS and non-manipulated Marinol.

j. The predictive value of in vitro studies and of human abuse potential studies can be validated only with the collection of epidemiological data after marketing of the product.

RECOMMENDATIONS

1- Upon consideration of the totality of the data (clinical and in vitro) submitted by the Sponsor, either under NDA or under the most recent supplemental submission, CSS continues to recommend rescheduling of SYNDROS from Schedule I to Schedule II of the CSA, if and when approved by the FDA.

2- CSS recommends that the Sponsor submit to FDA and implement a comprehensive postmarketing proposal to evaluate the levels of abuse and misuse of SYNDROS. If postmarketing data are supportive of rescheduling the product, Insys should consider petitioning the DEA, which ultimately makes decisions on scheduling under the Controlled Substances Act (CSA). If DEA accepts the petition, DEA can consult FDA for analysis of the postmarketing data collected to support a rescheduling petition under the CSA and provide an updated eight factor analysis.

Reference ID: 3952372

REFERENCES

Chaudry, H. R., Moss, H. B., Bashir, A., & Suliman, T. (1991). Cannabis psychosis following bhang ingestion. *Br J Addict, 86*(9), 1075-1081.

Hancock-Allen, J. B., Barker, L., VanDyke, M., & Holmes, D. B. (2015). Notes from the Field: Death Following Ingestion of an Edible Marijuana Product--Colorado, March 2014. *MMWR Morb Mortal Wkly Rep, 64*(28), 771-772.

Hudak, M., Severn, D., & Nordstrom, K. (2015). Edible Cannabis-Induced Psychosis: Intoxication and Beyond. *Am J Psychiatry, 172*(9), 911-912. doi: 10.1176/appi.ajp.2015.15030358

Mehrpour, O., Karrari, P., & Afshari, R. (2012). Recreational use and overdose of ingested processed cannabis (Majoon Birjandi) in the eastern Iran. *Hum Exp Toxicol, 31*(11), 1188-1189. doi: 10.1177/0960327112446814

Nicks, D. (2014, April 29, 2014). Colorado takes another look at pot edibles after deaths. *Time Magazine.* Retrieved March 2016

Sapienza, F. L. (2006). Abuse deterrent formulations and the Controlled Substances Act (CSA). *Drug Alcohol Depend, 83 Suppl 1*, S23-30. doi: 10.1016/j.drugalcdep.2005.11.028

Weiss, S. (2015). Edibles: for experts only? Ingesting marijuana, as opposed to smoking it, has come a long way since the days of homemade pot brownies. *State Legis, 41*(3), 23.

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/s/

SILVIA N CALDERON
06/28/2016

MARTIN S RUSINOWITZ
06/28/2016

MICHAEL KLEIN
06/29/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 205525	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Syndros (proposed 7/17/15) Established/Proper Name: dronabinol Dosage Form: oral solution Strengths: 4.25 mg/0.85 mL		
Applicant: Insys Development Company, Inc.		
Date of Receipt: 06/01/2015		
PDUFA Goal Date: 07/01/2016	Action Goal Date (if different):	
RPM: Maureen Dewey		
Proposed Indications: i) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and ii.) anorexia associated with weight loss in patients with AIDS.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Reference ID: 3950363

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 018651 **Marinol (dronabinol capsules) 5 mg**	**Indications** **Administration** **Contraindications** **Warnings and Precautions** **Adverse Reactions** **Drug Interactions** **Use in Specific Populations** **Drug Abuse and Dependence** **Overdosage** **Description** **Clinical Pharmacology** **Nonclinical** **Patient Counseling**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

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

- **FDA will rely on this study for bioequivalence**

RELIANCE ON PUBLISHED LITERATURE

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Marinol (dronabinol capsules) 5 mg	**NDA 018651**	**YES**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Reference ID: 3950363

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The application provides a change in Dosage Form from capsule to oral solution.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

`1

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

Reference ID: 3950363

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

Reference ID: 3950363

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

NDA 18561 Marinol (dronabinol capsules) same indications
ANDA 078292
ANDA 079217
ANDA 078501 discontinued

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ **21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)**

Patent number(s):

Reference ID: 3950363

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

MAUREEN D DEWEY
06/23/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 13, 2016
To:	Donna Griebel, MD Director **Division of Gatroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	SYNDROS (dronabinol), CX
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 205525
Applicant:	Insys Therapeutics, Inc.

1 INTRODUCTION

On June 1, 2015, Insys Therapeutics, Inc. resubmitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 205525 for SYNDROS (dronabinol) oral solution. The Reference Listed Drug (RLD) is NDA 018651, MARINOL (dronabinol) Capsules, held by AbbVie Inc. This resubmission is in response to a Refuse to File (RTF) letter issued by the Division of Gastroenterology and Inborn Errors Products (DGIEP) to Insys Therapeutics, Inc. on October 10, 2014 to the Applicant's August 12, 2014 original submission for NDA 205525.

The proposed indication for SYNDROS (dronabinol) oral solution is for the treatment 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by DGIEP on July 21, 2015, and September 2, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SYNDROS (dronabinol) oral solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on March 24, 2016.

2 MATERIAL REVIEWED

- Draft SYNDROS (dronabinol) oral solution PPI and IFU received on September 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 24, 2016.
- Draft SYNDROS (dronabinol) oral solution Prescribing Information (PI) received on September 28, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on June 9, 2016.
- Draft SYNDROS (dronabinol) oral solution Prescribing Information (PI) received on September 28, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on June 13, 2106.
- Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review for Syndros (dronabinol) Oral Solution 4.25 mg/0.85 mL (5 mg/ml) dated March 24, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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

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

/s/

KAREN M DOWDY
06/13/2016

MEETA N PATEL
06/13/2016

MARCIA B WILLIAMS
06/13/2016

LASHAWN M GRIFFITHS
06/13/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality
Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch

DATE:	October 26, 2015 Update: February 18, 2016 **Updated: March 21, 2016** **Updated: June 6, 2016**
TO:	Maureen Dewey, CDER/OND/ODEIII/DGIEP, WO22 RM5232 Maureen.Dewey@fda.hhs.gov Julie G. Beitz, CDER/OND/ODEIII/DGIEP, WO22 RM5214 Julie.Beitz@fda.hhs.gov Office of combination products at combination@fda.gov
Through:	For Francisco Vicenty, Branch Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3425
From:	Bleta Vuniqi, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429
Applicant:	Insys Therapeutics, Inc. 1333 South Spectrum Boulevard, Suite 100 Chandler, AZ, 85286 FEI# 3010878756
Application #	NDA 205525
Product Name:	Dronabinol Oral Solution
Consult	Evaluate the Dronabinol Oral Solution documents provided by the applicant on quality system requirement 21 CFR 820,

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.06.06 18:07:42 -04'00'

Instructions: and determine if an inspection of the manufacturing facilities is required.

Update: evaluate the firm's response to the deficiencies sent on October 26, 2015

Update: Evaluate the firm's response to the deficiencies sent on February 18, 2016

Update: Evaluate the inspection conducted at DPT Laboratories, Ltd.

Background:

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205525 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:

Dronabinol Oral Solution is supplied as a single size multi-dose container comprised of a 30 mL glass bottle with a 20-mm child-resistance cap. For tamper evidence, the bottle is wrapped with a PVC body band, and packaged in a suitable size carton along with a graduated oral dispenser for dose dispensing.

The proposed indication is for the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.



Table 1: 30 mL Bottle Control Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Overflow volume	Complies	Volumetric
Closure fit	Fits with the 20 mm child-resistant cap	Visual
Material verification	Clear Amber (b) (4) Glass	Visual verification and supplier CoA verification

Table 2: Child Resistant Cap Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Outer cap and inner shell material/color verification	Complies	Visual verification and CoA verification
Closure fit	Fits with the 30mL glass bottle	Visual
Identification of Teflon layer[a]	IR spectrum obtained for the sample has similar maxima and minima of IR absorption as the reference spectrum[b]	IR Spectroscopy

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

2. Based on the information provided, it could not be determined which facility was responsible for developing the design specifications of the device constituent part, and which facility is maintaining the design history file.

3. The description of the manufacturing activities of the finished combination product was not provided. The application did not include information on how and where the finished combination product would be assembled. No information was provided on acceptance activities.

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. With regards to information being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted. Also, more information will be needed from the applicant prior to making a decision about which facility or facilities would potentially need to be inspected.

Regulatory history evaluation

After reviewing the application, the (b) (4) site located at (b) (4) was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that a device inspection conducted on (b) (4), revealed multiple deficiencies and was classified VAI. The inspection focused on the OEM liquid dispenser [syringe] product. The following QSIT subsystems were covered during the inspection: Management Controls, CAPA, Design Controls, P&PC, Document Controls and Purchasing Controls. A 5-item form FDA 483 was issued to the firm at the conclusion of the inspection. The observations included CAPA, complaints, calibration, and document control.

Determination whether an inspection of the manufacturing facilities is required will not be made at this time until the firm provides the additional information related to the finished combination product manufacturing activities.

Update:

The firm confirmed (b) (4) located at (b) (4), is the primary supplier and manufacturer of oral dispenser and press in bottle adapter. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. FACTS revealed that the firm is listed a "not a workload obligation". The firm is registered with FDA as a "Manufacturer". The firm is not responsible for manufacturing the final combination product; therefore, an inspection is not required for this firm.

Additionally, the firm noted that the drug product manufacturer and the final combination product manufacturer is DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. The most recent inspection was performed on (b) (4). This inspection was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) No FDA-483, Inspectional Observations, was issued and the inspection was classified as NAI. The previous inspection of the firm was conducted on (b) (4). This was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4). This inspection covered the new facility, equipment, and process and associated controls including automation, analytical, environmental, microbiology, and formulation and testing of (b) (4). An FDA-483 was issued, and the inspection was classified VAI. The district recommended approval of ANDA (b) (4), ANDA (b) (4). An inspection was also conducted on (b) (4) and covered GMPs of sterile and non-sterile dosage forms, as well as Pre-Approval coverage for NDA (b) (4), (b) (4), filed to transfer manufacture and testing of the finished product to this site. This inspection is classified NAI and approval was recommended for NDA (b) (4). The firm is responsible for manufacturing the final combination product; therefore, an inspection is required for this firm.

Update: A pre-market approval inspection at DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701 was completed on June 1st, 2016. The inspection was classified as NAI, and no observations were noted.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application NDA 205525 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product and it is requested that the below be communicated to the firm:

1. Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

   A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (Management Controls, Design Controls, Purchasing Controls and Corrective and Preventive Actions).

   Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

   Firm’s response:

   The applicant noted that the combination product is manufactured at DPT Laboratories, Ltd. Therefore, the firm provided DPT procedures.

   Management Control (21 CFR 820.20):

   (b) (4)

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control (21 CFR 820.30):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.30.

Purchasing Controls (21 CFR 820.50):

(b) (4)

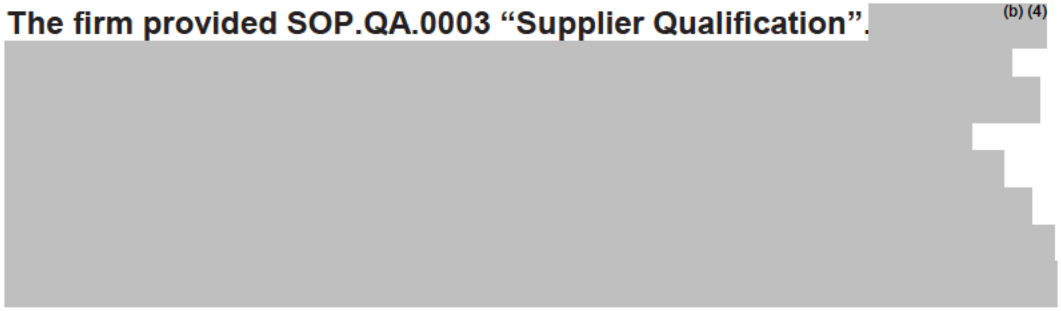


The information provided by the firm has inadequately addressed the requirements of 21CFR 820.50.

Deficiencies to be conveyed to the applicant:
Insys Therapeutics, Inc. is responsible for the final combination product. Your November 30, 2015 response noted (b) (4) " Please provide a description of your supplier evaluation process and a description of your purchasing controls.

Update: 03/21/2016 – Firm's Response

The firm provided SOP.QA.0003 "Supplier Qualification". (b) (4)



(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.50.

Corrective and Preventive Action (CAPA) (21 CFR 820.100):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.100.

2. In your response, please provide the name of the facility or facilities that perform the manufacture of the combination product and constituent parts including each facility's responsibility. Additionally, your response should include the facility that was responsible for developing the Dronabinol Oral Solution design specifications, and the facility that maintains the design history file for the finished combination product. Lastly, please provide the name of the facility or facilities that maintains the records for Design Controls; Corrective and Preventive Action; and Purchasing Controls.

Firm's response:

The applicant provided a table containing the name of the facilities that perform the manufacture of the commercial combination product and constituent parts, including each facility's responsibility.

Name of the facility	Responsibility
(b) (4)	Primary supplier of oral dispenser and press in bottle adapter
DPT Laboratories, Ltd. 1200 Paco Way Lakewood, NJ 08701	(b) (4) manufacturing, (b) (4) (b) (4) packaging and labeling, analytical release and alternate stability testing site – Syndros Oral Solution
(b) (4)	Primary supplier of clear amber (b) (4) glass 30 mL bottle
	Primary supplier of white polypropylene child - resistant cap lined with (b) (4) liner ((b) (4) liner coated with a Teflon film)
	Primary supplier of (b) (4) cap liner (b) (4) liner coated with a Teflon film) (b) (4)

The firm noted DPT maintains records of design controls or specifications, CAPA and Purchasing controls with oversight from Insys Therapeutics. DPT and Insys Therapeutics have a Quality Agreement in place.

3. The information provided was insufficient to verify that the acceptance activities conducted on supplied device constitutes parts to ensure the safety and effectiveness of the finished combination product. Additionally, the descriptions of the manufacturing activities of the finished combination product were not provided. The application did not include information on how the finished combination product would be assembled.

Firm's response:

Acceptance criteria for incoming controls performed by DPT site for the device components were included in NDA Section 3.2.R.4.6.

Table 5: Oral Dispenser Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification
Graduations Accuracy	(b) (4)	Gravimetric

Table 6: Press-in bottle adapter Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification

Device manufacturer ((b) (4)) performs the release testing on the device components prior to shipment to DPT. During the development, Insys Therapeutics also performed device functionality testing to confirm the suitability, safety and effectiveness of the finished combination product and results were provided in NDA (refer to Sections 3.2.R.4.3 and 3.2.R.4.4).

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application Dronabinol Oral Solution and has the following recommendations:

Application Dronabinol Oral Solution is approvable from the perspective of the applicable Quality System Requirements.

Bleta Vuniqi -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bleta Vuniqi -S, 0.9.2342.19200300.100.1.1=2000554108
Date: 2016.06.06 18:03:34 -04'00'

Bleta Vuniqi

Prepared: BVuniqi: October 26, 2015
Reviewed: VVerna: October 28, 2015
Revised: BVuniqi: February 29, 2016
Reviewed: VVerna:March 1, 2016
Revised: BVuniqi: March 21, 2016
Reviewed: VVerna March 21, 2016
Revised: BVuniqi: June 6, 2016
Reviewed: VVerna: June 6, 2016

CTS No.: ICC1500308

Response: CTS No.: ICC1600112

NDA 205525

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/s/

TRUONG D QUACH
06/07/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality
Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch

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DATE: October 26, 2015

Update: February 18, 2016

Updated: March 21, 2016

Updated: June 6, 2016

TO: Maureen Dewey, CDER/OND/ODEIII/DGIEP, WO22 RM5232

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Through: For Francisco Vicenty, Branch Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3425

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.06.06 18:07:42 -04'00'

From: Bleta Vuniqi, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429

Applicant: Insys Therapeutics, Inc.
1333 South Spectrum Boulevard, Suite 100
Chandler, AZ, 85286
FEI# 3010878756

Application # NDA 205525

Product Name: Dronabinol Oral Solution

Consult Evaluate the Dronabinol Oral Solution documents provided by the applicant on quality system requirement 21 CFR 820,

Instructions: and determine if an inspection of the manufacturing facilities is required.

Update: evaluate the firm's response to the deficiencies sent on October 26, 2015

Update: Evaluate the firm's response to the deficiencies sent on February 18, 2016

Update: Evaluate the inspection conducted at DPT Laboratories, Ltd.

Background:

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205525 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:

Dronabinol Oral Solution is supplied as a single size multi-dose container comprised of a 30 mL glass bottle with a 20-mm child-resistance cap. For tamper evidence, the bottle is wrapped with a PVC body band, and packaged in a suitable size carton along with a graduated oral dispenser for dose dispensing.

The proposed indication is for the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.

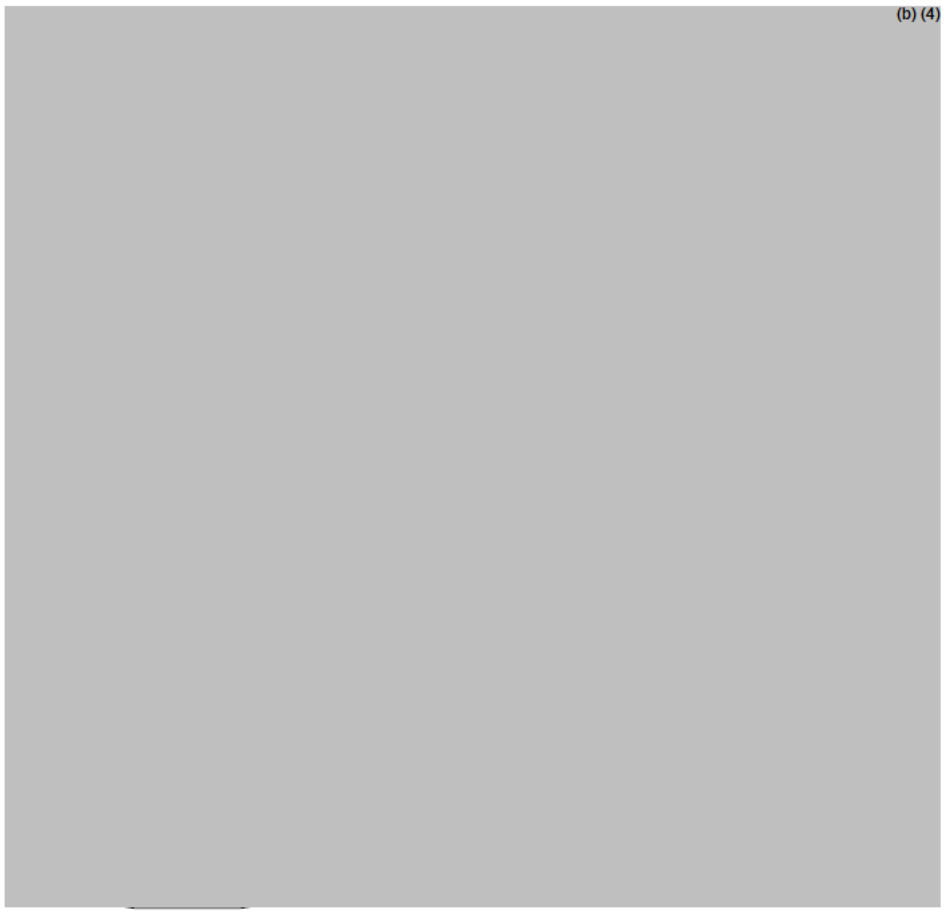


Table 1: 30 mL Bottle Control Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Overflow volume	Complies	Volumetric
Closure fit	Fits with the 20 mm child-resistant cap	Visual
Material verification	Clear Amber (b) (4) Glass	Visual verification and supplier CoA verification

Table 2: Child Resistant Cap Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Outer cap and inner shell material/color verification	Complies	Visual verification and CoA verification
Closure fit	Fits with the 30mL glass bottle	Visual
Identification of Teflon layer[a]	IR spectrum obtained for the sample has similar maxima and minima of IR absorption as the reference spectrum[b]	IR Spectroscopy

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

2. Based on the information provided, it could not be determined which facility was responsible for developing the design specifications of the device constituent part, and which facility is maintaining the design history file.

3. The description of the manufacturing activities of the finished combination product was not provided. The application did not include information on how and where the finished combination product would be assembled. No information was provided on acceptance activities.

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. With regards to information being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted. Also, more information will be needed from the applicant prior to making a decision about which facility or facilities would potentially need to be inspected.

Regulatory history evaluation

After reviewing the application, the (b) (4) site located at (b) (4) , was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that a device inspection conducted on (b) (4), revealed multiple deficiencies and was classified VAI. The inspection focused on the OEM liquid dispenser [syringe] product. The following QSIT subsystems were covered during the inspection: Management Controls, CAPA, Design Controls, P&PC, Document Controls and Purchasing Controls. A 5-item form FDA 483 was issued to the firm at the conclusion of the inspection. The observations included CAPA, complaints, calibration, and document control.

Determination whether an inspection of the manufacturing facilities is required will not be made at this time until the firm provides the additional information related to the finished combination product manufacturing activities.

Update:

The firm confirmed (b) (4) located at (b) (4), is the primary supplier and manufacturer of oral dispenser and press in bottle adapter. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. FACTS revealed that the firm is listed a "not a workload obligation". The firm is registered with FDA as a "Manufacturer". The firm is not responsible for manufacturing the final combination product; therefore, an inspection is not required for this firm.

Additionally, the firm noted that the drug product manufacturer and the final combination product manufacturer is DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. The most recent inspection was performed on (b) (4) This inspection was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) No FDA-483, Inspectional Observations, was issued and the inspection was classified as NAI. The previous inspection of the firm was conducted on (b) (4) This was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) This inspection covered the new facility, equipment, and process and associated controls including automation, analytical, environmental, microbiology, and formulation and testing of (b) (4) An FDA-483 was issued, and the inspection was classified VAI. The district recommended approval of ANDA (b) (4) ANDA (b) (4) An inspection was also conducted on (b) (4) and covered GMPs of sterile and non-sterile dosage forms, as well as Pre-Approval coverage for NDA (b) (4) (b) (4) filed to transfer manufacture and testing of the finished product to this site. This inspection is classified NAI and approval was recommended for NDA (b) (4) The firm is responsible for manufacturing the final combination product; therefore, an inspection is required for this firm.

Update: A pre-market approval inspection at DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701 was completed on June 1st, 2016. The inspection was classified as NAI, and no observations were noted.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application NDA 205525 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product and it is requested that the below be communicated to the firm:

1. Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

   A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (Management Controls, Design Controls, Purchasing Controls and Corrective and Preventive Actions).

   Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

   Firm’s response:

   The applicant noted that the combination product is manufactured at DPT Laboratories, Ltd. Therefore, the firm provided DPT procedures.

   Management Control (21 CFR 820.20):

   (b) (4)

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control (21 CFR 820.30):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.30.

Purchasing Controls (21 CFR 820.50):

(b) (4)

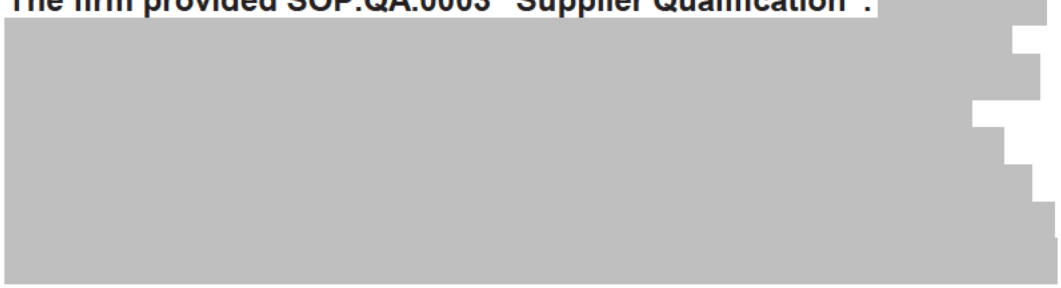


The information provided by the firm has inadequately addressed the requirements of 21CFR 820.50.

Deficiencies to be conveyed to the applicant:
Insys Therapeutics, Inc. is responsible for the final combination product. Your November 30, 2015 response noted (b) (4) " Please provide a description of your supplier evaluation process and a description of your purchasing controls.

Update: 03/21/2016 – Firm's Response

The firm provided SOP.QA.0003 "Supplier Qualification". (b) (4)



(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.50.

Corrective and Preventive Action (CAPA) (21 CFR 820.100):

(b) (4)

).

The information provided by the firm has adequately addressed the requirements of 21CFR 820.100.

2. In your response, please provide the name of the facility or facilities that perform the manufacture of the combination product and constituent parts including each facility's responsibility. Additionally, your response should include the facility that was responsible for developing the Dronabinol Oral Solution design specifications, and the facility that maintains the design history file for the finished combination product. Lastly, please provide the name of the facility or facilities that maintains the records for Design Controls; Corrective and Preventive Action; and Purchasing Controls.

Firm's response:

The applicant provided a table containing the name of the facilities that perform the manufacture of the commercial combination product and constituent parts, including each facility's responsibility.

Name of the facility	Responsibility
(b) (4)	Primary supplier of oral dispenser and press in bottle adapter
DPT Laboratories, Ltd. 1200 Paco Way Lakewood, NJ 08701	(b) (4) manufacturing, packaging and labeling, analytical release and alternate stability testing site – Syndros Oral Solution
(b) (4)	Primary supplier of clear amber glass 30 mL bottle
	Primary supplier of white polypropylene child - resistant cap lined with (b) (4) liner (b) (4) liner coated with a Teflon film)
	Primary supplier of (b) (4) cap liner (b) (4) liner coated with a Teflon film) (b) (4)

The firm noted DPT maintains records of design controls or specifications, CAPA and Purchasing controls with oversight from Insys Therapeutics. DPT and Insys Therapeutics have a Quality Agreement in place.

3. The information provided was insufficient to verify that the acceptance activities conducted on supplied device constitutes parts to ensure the safety and effectiveness of the finished combination product. Additionally, the descriptions of the manufacturing activities of the finished combination product were not provided. The application did not include information on how the finished combination product would be assembled.

Firm's response:

Acceptance criteria for incoming controls performed by DPT site for the device components were included in NDA Section 3.2.R.4.6.

Table 5: Oral Dispenser Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification
Graduations Accuracy	(b) (4)	Gravimetric

Table 6: Press-in bottle adapter Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification

Device manufacturer ([redacted] (b) (4)) performs the release testing on the device components prior to shipment to DPT. During the development, Insys Therapeutics also performed device functionality testing to confirm the suitability, safety and effectiveness of the finished combination product and results were provided in NDA (refer to Sections 3.2.R.4.3 and 3.2.R.4.4).

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application Dronabinol Oral Solution and has the following recommendations:

Application Dronabinol Oral Solution is approvable from the perspective of the applicable Quality System Requirements.

Bleta Vuniqi -S

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Bleta Vuniqi

Prepared: BVuniqi: October 26, 2015
Reviewed: VVerna: October 28, 2015
Revised: BVuniqi: February 29, 2016
Reviewed: VVerna:March 1, 2016
Revised: BVuniqi: March 21, 2016
Reviewed: VVerna March 21, 2016
Revised: BVuniqi: June 6, 2016
Reviewed: VVerna: June 6, 2016

CTS No.: ICC1500308

Response: CTS No.: ICC1600112

NDA 205525

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

/s/

MAUREEN D DEWEY
06/07/2016

M E M O R A N D U M

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

Date: April 22, 2016

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Silvia N. Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 205-525 for Dronabinol Oral Solution (Oral solution: 150 mg/30 mL, or 4.25 mg/0.85mL delivered dose) Scheduling Recommendation Dispute Resolution

Materials Reviewed: DARRTS, NDA 205-525: SYNDROS (Dronabinol Oral Solution), Sequence N0. 0023: Response to Information Request, 3/10/2016

I. SUMMARY

1. Background

Upon review of all data related to the abuse of the Dronabinol Oral Solution (SYNDROS) provided by the Sponsor under the NDA 205-525, we determined that SYNDROS should be rescheduled from Schedule I to Schedule II of the Controlled Substances Act (CSA). Our review can be found in DARRTS, NDA 205525, Calderon, Silvia N., 2/26/16.

On March 2, 2016, the CSS Team and members of Division of Gastroenterology and Inborn Errors Products (DGIEP) contacted Insys Therapeutics, Inc. (the Sponsor) via telecom to convey our findings and recommendation for scheduling. The Sponsor was also informed about their recourse to dispute our findings. A list of technical findings discussed on the telecom was sent to the Sponsor on March 4, 2016. The Sponsor responded to these technical points on March 10, 2016 (DARRTS, NDA 205525, Sequence 0023, 3/10/2016), including new in vitro study results. This memorandum provides general conclusions regarding the abuse potential of SYNDROS in relation to that of Marinol capsules (See

Conclusions Section), which responds to each of the Sponsor's claims provided under the specific points discussed on March 2, 2014 (See Recommendations section), and discusses the technical aspects of the new studies conducted by the Sponsor (See Discussion section).

In the March 10, 2016, amendment to the application, the Sponsor submitted study results from additional extraction studies and vaporization studies using the previously selected solvents for extraction, the same type of e-cigarette used in previous studies and the Volcano for vaporization studies. For these additional studies, the Sponsor did not change the experimental conditions of the studies and the only change introduced was the weight and concentration of the Marinol samples used in the studies. A larger sample of Marinol and of a higher concentration was used in the three studies. In other words, instead of using samples of Marinol and SYNDROS with equivalent dronabinol content on mg per mg basis, the Sponsor chose to use equal sample volumes. Thus, the Sponsor used for the three studies 1 mL of the Marinol 10 mg capsule formulation that was obtained by puncturing each Marinol capsule with the point of small pair of scissors, and squeezing the content of 7 Marinol 10 mg capsules, and 1 mL of SYNDROS. Average samples of Marinol contained 55 mg of dronabinol, whereas the SYNDROS sample contained 5 mg. Thus, equivalent amounts of dronabinol were not compared; rather the amounts were 11 to 1 from the Marinol and SYNDROS formulations, respectively. (See Table 1, Table 2 and Table 3 under the Discussion section for a description of the experimental conditions selected for the new studies).
The Sponsor claims that the abuse potential of SYNDROS is not different than that of Marinol capsules (Schedule III) and that contrary to our findings; both formulations have similar physicochemical properties.

CONCLUSIONS

This section summarizes the key findings that continue to support our recommendation to reschedule SYNDROS from Schedule I to Schedule II of the CSA upon approval. After reviewing **all data related to the abuse potential of SYNDROS** provided in the application (NDA 205,525), Sponsor's written responses to our concerns, as discussed during the March 2, 2016 telecom, and supplemental data provided by the Sponsor, we conclude:

1- **Scheduling recommendations are based on the overall assessment of the abuse potential of a substance. The chemistry, pharmacology, clinical data, pharmacokinetics and pharmacodynamic effects, and reports of actual abuse are relevant to the substance being considered for scheduling. Because of their common API, SYNDROS shares properties with marijuana (Schedule I) and Marinol (Schedule III), as described below. Because SYNDROS' ease of abuse by a number of routes and ease of manipulation of the alcoholic solution by a number of in vitro processes, the overall CSS evaluation of the abuse potential of SYNDROS raises concerns about the risks of abuse that are closer to those of marijuana (a Schedule I substance) and not Marinol (Schedule III), which has not shown itself to be widely abused.**

2- **SYNDROS oral solution and Marinol capsules contain the API: Dronabinol or delta-9-tetrahydrocannabinol, the principle psychoactive component of marijuana. Thus, SYNDROS oral solution and Marinol capsules present the same pharmacological effects and**

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similar pharmacokinetics. However, the formulations differ in their chemical and physical properties. Formulation differences account for differences in abuse potential, because the formulation properties can impact the routes of abuse, actual abuse of the product, patterns of abuse and adverse effects associated with the ways the product is abused.

a. **SYNDROS can be easily abused orally without any manipulation of the formulation and through the inhalation route upon manipulation of the formulation.**

b. **No manipulation of SYNDROS is necessary to ingest the large amount of dronabinol present in the product, as abusers may ingest the alcoholic sweetened solution of delta-9-THC directly from the dispensed container.**

3- Delta-9-THC-containing products in the form of edibles and drinks are being abused orally.

Oral abuse is emerging in states where the use of marijuana is legalized and available in the form of edibles and drinks.

NIDA's Monitoring the Future survey 2014[1] (MTF) revealed that the consumption of marijuana edibles is more prevalent in states that permit the use of marijuana for medical purposes. Specifically, this survey showed emergence of a new pattern of abuse: 40 percent of 12th graders (17- 18 years old) who consumed marijuana in the past year reported being consumers of edible marijuana in the medical marijuana states versus 26 percent in the non-medical marijuana states. The 2015 MTF showed a similar pattern of abuse of marijuana edibles (Johnston, 2016)[2].

The 2014 Summer Styles[3] survey indicates that the majority of current marijuana users (past month users) had consumed marijuana for recreational purposes and that although the majority seems to prefer the combusted use of marijuana, approximately 16 percent of the current users report consuming edibles or drinks (Schauer, 2016).

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[1] Monitoring the Future is a national survey that tracks drug use prevalence and trends among adolescents in the United States. MTF is reported annually by the Institute for Social Research at the University of Michigan under a grant from NIDA. Every spring, MTF surveys 8th, 10th, and 12th graders in randomly selected U.S. schools. MTF has been conducted since 1975 for 12th graders and since 1991 for 8th and 10th graders. The MTF survey presents data in terms of prevalence among the sample interviewed. For 2015, the latest year with complete data, the sample sizes were 15,000 – 8th graders; 16,100 – 10th graders; and 13,700 – 12th graders. In all, a total of about 44,900 students of 382 schools participated in the 2015 MTF.

[2] As of 2015 , the following states are classified as medical marijuana for the analyses presented: AK, AZ, CA,CO, CT, DC, DE, HI, IL, MA, MD, ME, MI,MN,MT,NU,NV,NJ,NM, NY,OR, RI,VT, and WA

[3] The Summer Styles survey is a seasonal national representative consumer panel survey of adults aged 18 year old or older, conducted by Porter Novelli Public Services. Summer Styles assesses health-related indicators among U.S. adults aged ≥18 years, and draws from GFK's Knowledge-Panel, an online panel initiated in 1999 that uses probability based sampling to reach respondents regardless of landline phone or internet access. The survey collects information about the current mode of use of marijuana, as indicated by the mode of use in the past 30 days, and lifetime mode of use of marijuana. In addition, the survey includes questions to address the reason for use of marijuana (medical, recreational or both). Participants were recruited and completed the survey online. A total of 4,269 participants completed the survey during June-July 2014.

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4- New information submitted by the Sponsor does not alter the conclusions in our February 26, 2016, review (Section 1.2.2, pp 11-13) with respect to the ease of obtaining concentrates from dronabinol oral solution for non-oral routes of abuse. In vitro evaporation studies (drying studies) showed that the alcoholic component of SYNDROS is readily volatilized when exposed to minimal heat, affording concentrates that can be used for smoking or vaping. Depending on the method, a 3 to 7 fold reduction in volume of SYNDROS can be achieved (a 5-fold reduction would give an evaporated solution that is 25 mg delta-9-THC per mL), whereas Marinol can't be concentrated.

5- Data from the Sponsor's new extraction studies confirm study results from prior studies and show that the efficiency of extraction of dronabinol from SYNDROS is approximately 90 %. Based on the study results presented by the Sponsor it can be predicted that nearly all of the dronabinol contained in the 30 mL of the dispensed product are easily extractable. These data are predictive of potential manipulation of the product after marketing. Validation would be expected from postmarketing data.

6- The Sponsor concludes that one mL of the dronabinol in sesame oil 10 mg formulation provides 10.5 times the amount of dronabinol after extraction when compared to 1mL of SYNDROS. These results are consistent with the fact that the initial sample contained approximately 10.5 times more dronabinol than the SYNDROS sample.

7- The in vitro experiments predict that manipulation of SYNDROS for obtaining samples for vaporization is feasible and more effective than when using Marinol capsules. In vitro data also shows that more than 20 % of the Marinol sample is lost in the manipulation process. The Sponsor did not use standardized THC samples to validate the conditions of the vaporization studies with e-cigs or the Volcano vaporizer, and did not conduct studies using extracts or concentrates.

a. The new study conducted by the Sponsor using the Volcano doesn't add new information; it confirms that under the conditions selected approximately between 3 and 4 % of dronabinol is recovered from SYNDROS, whereas **none or 0.1 %** of dronabinol is recovered from the sesame oil.

b. When using an e-cig, the Sponsor concludes that a higher amount of dronabinol can be delivered when using 1 mL of the 10 mg sesame oil formulation containing approximately 55 mg of dronabinol than 1 mL of the Oral Solution containing 5 mg of dronabinol.

8- Although it could be argued that SYNDROS and Marinol can be abused orally in a similar way, Marinol is available in individual units of variable strengths (2.5 mg, 5 mg and 10 mg of delta-9-THC) whereas SYNDROS provides a large amount of delta-9-THC and 15 mL of

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alcohol (50 % w/w alcoholic solution) in a solution that could easily be taken in its entirety as opposed to individual doses.

a. **A shot glass of SYNDROS taken as if it were an alcoholic beverage would, provide not only a larger amount of alcohol than an equivalent volume of vodka (30 mL of 40 % vodka provides 12 mL of alcohol), but a very large amount of delta-9-THC, taken in a manner that will be perceived differently than if it were taken in the form of capsules.**

b. **SYNDROS provides 150 mg of dronabinol (bioequivalent to 176 mg of dronabinol in sesame oil). Thus, to consume 176 mg of Marinol an individual would have to consume 70 Marinol 2.5 mg capsules, 35 capsules of Marinol 5 mg capsules or 17-18 Marinol 10 mg capsules.[4] Thus, the high dronabinol content in SYNDROS adds to the risk of adverse outcomes from abuse and misuse of the solution.**

   In addition, it is unknown if the 15 mL of alcohol present in 30 mL of the formulation will potentiate the effects of the large amount of dronabinol present in the formulation.

c. When ingesting delta-9-THC containing products, individuals cannot predict the intensity of the effects that usually occur within 3 or 4 hours after ingestion. Considering that CNS adverse reactions are dose-related, and that in antiemetic studies significant CNS symptoms that included amnesia, confusion, delusions, and hallucinations were observed following oral doses of 0.4 mg/kg, significant CNS effects are expected if an individual would ingest the 150 mg of delta-9-THC present in SYNDROS.

9- Several cases of delta-9-THC unintentional overdoses from eating delta-9-THC- containing products are reported in the peer review literature. These cases required hospitalization and treatment, and in one case resulted in death of the individual. (Chaudry, Moss, Bashir, & Suliman, 1991; Hancock-Allen, Barker, VanDyke, & Holmes, 2015; Hudak, Severn, & Nordstrom, 2015; Mehrpour, Karrari, & Afshari, 2012; Nicks, 2014; Sapienza, 2006; Weiss, 2015).

10- Symptoms of a delta-9-THC overdose include paranoia, hallucinations, delusions, tachycardia, impaired motor ability, which can last for hours and result in hospital emergency room admissions.

RECOMMENDATIONS

1- After consideration of the totality of the data (clinical and in vitro) submitted by the Sponsor, both under the NDA or under the most recent supplemental submission, upon approval of

[4] Marinol capsules contain API formulated in sesame oil, available in 2.5 mg, 5 mg and 10 mg strengths, and are supplied in bottles of 25 and 60 capsules per bottle.

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the NDA, CSS recommends rescheduling of SYNDROS from Schedule I to Schedule II of the CSA.

2- CSS's initial discussion points raised during the March 2, 2016, telecom are numbered and listed below in *italic font*, followed by the Sponsor's response in regular font, and by **CSS's responses to be conveyed to the Sponsor in bold.**

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

Insys' responses to each item in Question #1 are discussed below.

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

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

CSS Response:

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

In the video provided, you show that it took less than 1 minute to collect 1 mL of the sesame oil formulation by pinching and squeezing seven 10 mg Dronabinol capsules. You report that 93-97% of the content of the capsules is collected in this manner. However, your analysis does not consider the amount (mg) of sample lost in the manipulation of the sample. You report that the

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average amount of dronabinol contained in 1 mL of the sample is 54.85 mg. Considering that 54.85 mg of dronabinol are recovered from a sample that contains a total of 70 mg of dronabinol (7 capsules of Marinol 10 mg strength), 21% percent of the sample is lost in the initial manipulation process.

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

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

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

CSS Response:

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

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

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

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

Reference ID: 3921488

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

CSS Response:

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

Under the new experimental conditions percent extraction of dronabinol increased from 85% to 95% when working with the oral solution and increased from 66 % percent to 73 % overall yield when using Marinol capsules. You reported a 93.5% extraction yield when working with the Marinol capsules, however this calculation does not take into consideration that when working with the Marinol capsules, on average, 21. 5 percent of the sample was lost in the handling process of the sesame oil formulation.

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

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

Insys Response:
Insys does not agree that SYNDROS oral solution has more abuse potential than Marinol due to the inherent PK/PD properties of the Product. The active moiety has not been structurally or chemically modified in any way that would result in different PK/PD characteristics. Further, it should be noted that

Insys demonstrated bioequivalence between two products via an adequately conducted clinical trial (INS-12-015), confirming similar PK/PD characteristics for both products.

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

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

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

CSS Response:

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

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

3. Physical manipulation of the Product is easier than with Marinol. Removing the formulation, either from the Product dispenser or extracting the sesame oil formulation from the capsules, would be the first step in physical manipulation for purposes of abuse. In vitro studies demonstrated that it is easier and more efficient to remove the dronabinol solution from the Product dispenser than to remove the

sesame oil formulation from capsules. Although you did not conduct specific studies to show this difference, a loss of approximately 30 % recovered API was reported in the preparation of the sesame oil sample for the drying studies. As part of the drying studies, the content of one capsule of Marinol was taken up by syringe, and the amount of API recovered from the sample was measured. Although the sample was not subject to any further manipulation, a high percentage of the API was lost in the process. The loss of recovered API may be explained by the loss of the sesame oil formulation due to the adherence of the oil to any instrument used to handle the samples.

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

Therefore, physical manipulation of Dronabinol capsules to recover its liquid content is relatively as easy as SYNDROS oral solution. In the drying studies, the shortest duration for drying time for 2 mL of SYNDROS oral solution was 7 min when using a microwave. In 7 min all 60 capsules in a bottle of Marinol can be opened and the content recovered. Using 10 mg capsules, that would provide 465 mg dronabinol (based on at least 93% recovery of capsule content) for abuse compared to 5 mg from SYNDROS oral solution in terms of total amount recovered by physical manipulation (see Table 1 below). These data suggest that Marinol capsules have greater potential for abuse than does SYNDROS.

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

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

CSS Response:

Your finding is not relevant. The 150 mg of dronabinol (bioequivalent to 176 mg of dronabinol as supplied in Marinol capsules) contained in SYNDROS are immediately available for consumption

by an abuser. SYNDROS can be drunk quickly without any prior manipulation. You haven't performed a test to dispute the pleasant sweet alcoholic flavor.

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

Insys Response: Insys does not agree with the Agency's assertion that Insys' smoking and vaping studies have major deficiencies. As stated earlier, the Information Request dated December 30, 2015, contained a request to conduct studies to assess the feasibility of vaping the oral solution and the contents of the Marinol capsules, as well as the reconstituted product extracts using a representative electronic cigarette device (E-cigs) as well as using other vaporizers such as the Volcano. There are no standards for conducting these types of trials and Insys had one month to research the available devices on the market for abusers, obtain the devices, familiarize yourselves with their use, determine how to conduct these trials, conduct the studies, and provide the Agency with the results. Insys tried to replicate the conditions that an actual abuser would use and not those carefully developed conditions of a research laboratory for vaporizing.

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

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

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

b. You evaluated the feasibility of using traditional cigarettes spiked either with the Product solution or the content of Marinol capsules, and you concluded that it was not possible to smoke either preparation. However, these studies, including the methods used to apply the extracted dronabinol to the cigarette

and the conditions used to simulate smoking, were not adequately described. Also, there was no comparison using a tobacco cigarette alone with the same methods, in order to provide assurance that the methods had the potential to administer dronabinol by measuring nicotine administration for all samples.

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

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

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

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

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

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

If the carefully developed techniques used in the Solowij publication are used on both products after extraction, the fact that approximately 51 mg of dronabinol can be extracted from 1 mL of Dronabinol capsule content versus 4.75 mg of dronabinol extracted from 1 mL of SYNDROS oral solution makes capsules more likely to be abused using the volcano vaporizer and Solowij techniques. However, these studies demonstrate that the use of the Volcano is not a viable method of abusing either SYNDROS or Dronabinol capsules because very small amounts of dronabinol are recovered in 25-30 minutes of vaporization.

CSS Response:

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

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

Insys Response: On December 30, 2015, Insys received a Request for Information that asked "to conduct studies to assess feasibility of vaping oral solution and the contents of the Marinol capsules using representative electronic cigarette devices (E-cigs)". There are no Guidance documents concerning the conduct of these studies. Based on this request, Insys evaluated several commonly used E-cigs for their ability to produce visible smoke. Appearance of visible smoke is how E-cigs are checked by the user for vaping. That is how an abuser will assess if an E-cig is working. This was also confirmed by conversations with regular E-cig users at the local vaping supply stores. The E-cigs evaluated were Subox Mini, Cannastick, Pinnacle Pro, Ambassador Kit V4 and Vaporesso. E-cigs with cotton and silica wick did not work as the atomizers burned due to over-heating when used for these two products. These types of E-cigs would be unsuitable for an abuser as atomizers would have to be replaced frequently adding to the cost of using such a device. Vaporesso was used in all the experiments because it produced smoke for both products. Wattage used for the experiments was recorded in the reports. For simulation

of smoking, the E-cig was attached to a vacuum source and smoke was passed through an ethanol solvent trap to trap dronabinol in ethanol. This procedure was described in the report. Validation of the method was addressed by the screening of several E-cigs to choose the one that allowed for visual confirmation through the appearance of smoke with these products. Not all the E-cigs have wattage control. The ones that provided wattage control, wattage was used where atomizers did not short out after each use and where the units did not overheat. The Vaporesso brand of E-cig uses a ceramic wick that was found to be most suitable for use with these products. The wattage was selected based on the E-cig generating consistent smoke for vaping from each product and at the same time not overheat.

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

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

CSS Response:

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

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

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

confers a much lower risk due to unintentional (or intentional) overdose for individuals likely to abuse SYNDROS. Consequently, dose related adverse effects due to overdose would be expected to be greater with the 600 mg of Marinol accessed from a single 60 count bottle of 10 mg capsules in contrast to the 4-fold lower total dose of 150 mg accessed from a single bottle of SYNDROS. Thus, the risk of overdose associated with Marinol is higher than that associated with SYNDROS.

CSS Response:

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

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

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

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

SYNDROS, with no statistical significance. In the totality of the data from this study, it shows that both substances were very similar in the responses elicited to measures related to abuse potential. Overall, the incidence of the adverse events in Table **2** were comparable between the treatment administered at the same dose level
(Marinol 10 mg vs. SYNDROS oral solution 10 mg and Marinol 30 mg vs. SYNDROS oral solution 30 mg). Comparable results are also observed for the psychiatric AEs across all studies conducted as depicted in Table 3 below.

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

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

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

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

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

[a]Integrated Summary of Safety, NDA 205525
[b]Previous test formulation of Dronabinol Oral Solution

CSS Response:

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

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

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

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

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

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

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

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

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

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

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

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

Insys Response: While drugs can certainly be abused by other routes, the primary objective of the current study was to evaluate the abuse potential of SYNDROS oral solution when ingested. Absorption while in the mouth can in part be mediated by sublingual absorption as well as by GI absorption, particularly because a portion of the drug with saliva is swallowed. Generally, sublingual administration is also mediated more readily when tablets or solid dosage forms are kept under the tongue compared to a liquid, as the dosage form remains intact long enough to be held under the tongue. With an oral solution, the length of time that the solution could be held under the tongue without swallowing would be comparably shorter than that of a solid dosage form. With attempts to hold the solution under the tongue, it is expected that a large proportion of the solution would be inevitably swallowed and thereby absorbed by the stomach/GI. The maximum amount of volume that can be comfortably retained in the sublingual pocket is reported to be in the range of about 0.4 mL. In this case, dronabinol was administered as an oral solution directly into the mouth using a syringe. Attempts to hold a solution under the tongue would be expected to be in short duration and highly variable with the degree of swallowing and time to first swallow. Sativex, an oromucosal spray containing THC and CBD, is marketed in the United Kingdom and Canada by G Pharmaceuticals. Each mL of Sativex contains 27 mg of dronabinol and 25 mg of CBD in 50 % ethanol and (b) (4) % propylene glycol. It should be noted that even with smaller volumes of highly concentrated alcohol spray (approximately 5-fold higher concentration than SYNDROS) administered oromucosally, the Tmax for THC is 1 hour (Sativex, Summary of Product Characteristics, May 20, 2015; GW Pharma) Consequently, the sublingual route of administration presents a much lower potential for abuse for SYNDROS relative to Marinol, when compared to the current preferred method, smoking.

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CSS Response:

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

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

DISCUSSION

Based on the data discussed between FDA and the Sponsor via a Telecom on March 2, 2016, the Sponsor conducted additional extraction studies, and vaporization and smoking studies.

Extraction Studies (Report CH0030, Protocol CHP16015, March 7, 2016)

The Sponsor repeated extraction studies using higher volumes of extraction of the selected extracting solvents to extract dronabinol from a larger and of a higher concentration sample of the dronabinol in sesame oil formulation and from a smaller sample of the Dronabinol Oral Solution. **Table 1** summarizes the experimental conditions used by the Sponsor in the most recent studies and in prior studies, and data from these studies.

Under the new conditions, instead of using samples of SYNDROS and of the Marinol formulation in mg per mg equivalent amounts, as the Sponsor did in prior studies, the Sponsor used equal sample volumes. As shown in **Table 1**, in the new studies the Sponsor utilized 10 mL of the extracting solvent (methylene chloride or ethanol), 1 mL of the Dronabinol Oral Solution (5 mg/mL) and 1 mL of the capsule contents from punctuating and squeezing seven Marinol 10 mg capsules. The Sponsor reports obtaining a sample that contains 60 mg of dronabinol in 1 mL of sesame oil formulation. The same extraction solvents as in previous studies were used; methylene chloride to extract dronabinol from the Oral Solution and ethanol to extract dronabinol from the sesame oil preparation. Under the new conditions the Sponsor used the same vortexing time of 60 seconds, and allowed the same time of organic layer separation (15 minutes after centrifugation at 4000 rpm). Upon extraction the solvents were evaporated recording the required

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drying times and upon evaporation the residues were taken in ethanol and the amount of dronabinol extracted was determined by HPLC. Studies were conducted by duplicate.

Under the prior conditions using 2 mL of the Oral solution and 2 mL of methylene chloride the Sponsor reported extracting 85 % of the dronabinol in the sample. Under the new conditions the 10 mL of methylene chloride were evaporated in 40 minutes (samples were dried for 50 minutes under the prior conditions). Under the new conditions of the study the Sponsor extracted on average 95 % of dronabinol from the Oral Solution.

When extracting dronabinol from the sesame oil formulation the Sponsor used 1 ml of the sesame oil formulation (containing on average 54.87 mg of dronabinol (Report-CH 0030, page 4 of 5, Table 5: Results for Dronabinol Capsule Extraction Studies using Ethanol) obtained by puncturing Marinol capsules with a scissor or a sharp needle, and squeezing the content of 7 Marinol 10 mg. *Of note: The average amount of dronabinol contained in 1 mL of the sample obtained by the Sponsor is reported to be 54.85 mg. Considering that 54.85 mg of dronabinol are recuperated from a sample that contains a total of 70 mg of dronabinol (7 capsules of Marinol 10 mg strength), 21 % percent of the sample is lost in the initial manipulation process. The Sponsor claims that it took them less than a minute to go through this procedure.*

Table 1: In Vitro data from extraction studies. Highlighted cells show main differences between the experimental conditions used in prior and in the most recent studies

	DATA FROM STUDIES SUBMITTED IN MARCH, 2016		**DATA FROM STUDIES SUBMITTED IN JANUARY 2016**	
	SYNDROS 1 ml	DRONABINOL CAPSULES 1 mL from 7 Dronabinol 10 mg capsules	SYNDROS 2 mL	DRONABINOL CAPSULES 660 mg of sesame oil formulation from 50 Dronabinol 2.5 mg capsules
Average amount of dronabinol, in mg (% manipulation efficiency)	5 mg (100 %)	54.85 mg (78.4 %)	10 mg (100%)	10 mg (8 %)
Extraction Solvent	10 mL Methylene Chloride	10 mL Ethanol	2 mL Methylene Chloride	2 mL Ethanol
Agitation and Layer Separation	Vortexed (1 min) Separation after centrifugation for 15 min. at 4000 rpm	Vortexed (1 min) Separation after centrifugation for 15 min. at 4000 rpm	Vortex (1 min) Separation after allowing sample to rest for 45 min.	Vortex (1 min) Separation after allowing sample to rest for 30 min.
Drying Time	40 min	150 min	50 min	75 min
Appearance of Dried Residue	Clear, colorless viscous residue	Clear, pale yellow viscous	Clear, colorless viscous residue	Clear, pale yellow viscous residue

		residue		
Avg. Dronabinol extracted (mg)	4.75 mg	51.11 mg	8.87 mg	6.57 mg
% Dronabinol Recovered from Initial Sample Weight	95 %	93 %	89 %	66 %
% Dronabinol Recovered from Formulations	95 % (From 5mg)	73 % (From 70 mg, 7 x 10 mg capsules)	88.7 %	5.25 % (From 125 mg, 50 x2.5 capsules)

Upon extraction and evaporation of the solvent, which took approximately 2 hours and a half, the Sponsor recuperated on average 93 % of the sample (51.1 mg out of 54.85 mg). Under the prior extraction conditions (samples were vortexed for 60 seconds, allowed to separate for 30 minutes and dried for 75 minutes) the Sponsor reported extracting 65.5 % of the theoretical amount of dronabinol when using ethanol. Considering the amount of dronabinol lost in the initial manipulation of the samples, and amount of dronabinol extracted from the sample, the overall extraction yield of dronabinol from the Marinol capsules is 73%.

Conclusions:

1- Under the new experimental conditions percent extraction of dronabinol increased from 85 % to 95 % when working with the oral solution and from 65.5 % percent to 73. 5 %overall yield when using Marinol capsules. The Sponsor reported a 93.5 % extraction yield when working with the Marinol capsules, however this calculation does not take in to consideration that when working with the Marinol capsules, on average, 21. 5 percent of the sample was lost in the handling process of the sesame oil formulation.

2- Longer drying times were observed to evaporate the ethanol extracts than the methylene chloride extracts (40 minutes vs 150 minutes).

3- The Sponsor concludes that 1 mL of dronabinol in sesame oil formulation provides 10.5 times the amount of dronabinol after extraction when compared to 1mL of Dronabinol Oral Solution. These results reflect the fact that the initial sample, not accounting for the 21 % loss of sample, contained approximately 10.5 times more dronabinol than the Dronabinol Oral Solution sample.

   This study confirms that the amount of dronabinol extracted when expressed in mg of recovered dronabinol depends on the initial amount of dronabinol present in the sample, and that the overall efficiency of the extraction process is in the 90 % range when working with the oral solution and in the 73 % range when working with the capsules. The overall extraction efficiency of 90 %, using methylene chloride with the oral solution, is more significant as a result than the Sponsor's compared results, which simply reflect the different starting amounts of dronabinol in the two 1 mL samples.

4- The Sponsor further concludes that Dronabinol capsules can be successfully manipulated to highly concentrated extracts in solvents that can be easily evaporated to give high content of dronabinol residues that can be abused by smoking or through other routes of abuse.

The extraction data presented by the Sponsor, despite sample losses and higher drying times, demonstrate that in fact dronabinol can be extracted from Marinol capsules and can successfully be extracted from the Dronabinol Oral solution. Based on the study results presented by the Sponsor it can be predicted that close to the totality of the dronabinol contained in the 30 mL of the dispensed product could be easily extracted. These data are predictive of potential manipulation of the product, and can only be validated by postmarketing data.

In vitro vaporization studies (Report. CH 0029, Protocol CHP16014, March 7, 2016).
The Sponsor conducted additional vaporization studies using e-cigarettes and the Volcano vaporizer.

- ***Vaporization studies using e-cigs***

In the cover letter dated March 10, 2016, the Sponsor claims that clearomizers, which contain a heating coil and wicks did not work in their hands. ((b) (4) . Thus, the Sponsor repeated smoking studied using the same type of e-cigarette used previously (Vaporesso 75VT E-cig).

Table 2 summarizes the experimental conditions used by the Sponsor in the most recent studies and in prior studies, and data from these studies. The only variable the Sponsor changed under the new conditions of the studies was the amount of dronabinol and strength of the dronabinol sesame oil formulation used for sample preparation. In prior studies the Sponsor had used 660 mg of the sesame oil formulation containing an equivalent amount of 10 mg or 40 mg of dronabinol depending on whether the sample was taken from 2.5 mg or 10 mg Dronabinol capsules (between 10 to 12 capsules). In this case 1 mL (average weight 905.15 mg) of the sesame oil formulation collected from 7 capsule of Marinol 10 mg was used in the experiments. Current and prior studies were conducted with 1 mL of the Oral Solution.

Table 2: In Vitro data from Vaporization Studies using the Vaporesso 75 VTC E-cig and by Direct Application of the Formulations Directly to the E-Cig Chamber. Highlighted cells show main differences between the experimental conditions used in prior and the most recent studies.

	DATA FROM STUDIES SUBMITTED IN MARCH, 2016		DATA FROM STUDIES SUBMITTED IN JANUARY 2016	
	SYNDROS 1 mL	DRONABINOL CAPSULES 1 mL (from 7 Dronabinol 10 mg capsules)	SYNDROS 1 mL	DRONABINOL CAPSULES 660 mg of sesame oil formulation from several Dronabinol 2.5 mg capsules
Average amount of dronabinol, in mg (% manipulation efficiency)	5 mg (100 %)	Approximately 60 mg- exact content not reported	5 mg (100%)	Approximately 10 mg- exact content not reported
Wattage	20	30	20	30
Average Vaping Time	16 min	22 min	18 min	12 min
Average Trap Solvent	2.1 mL	2.1 mL	2.8 mL	3.4 mL
Smoke appearance	Thin white smoke	Thin white smoke	Thin white smoke	Thin white smoke
Avg. Dronabinol recovered (mg) (% Recovered from initial sample)	0.088 mg (1.8 %)	2.444 mg (4 %)	0.099 (2.0%)	0.324 (3.2 %)

As in prior conditions, the samples were applied directly to the e-cig device chamber, smoke/vapors were collected using vacuum to simulate smoking, and trap using a 5 mL of ethanol, to further analyze the amount of dronabinol collected by HPLC. Samples were vaporized using the same wattage as before (20 for the Oral Solution and 30 for the Marinol sample). The new conditions did not change the amounts of dronabinol recuperated from the Marinol formulation percentage wise. In prior studies the Sponsor reported recovering 3.2 % of the dronabinol present in the Marinol sample, whereas in the current study 4 % of the dronabinol was recovered from the high strength capsule sample.
As reported previously, the percentage of dronabinol recovered from the Oral solution remained in the 1.8- 2 % range.

Reference ID: 3921488

Conclusions

1. The new studies confirmed that the amount of dronabinol recovered in the vapors when using e-cigarettes and by direct application of the formulation depend on the initial concentration of the sample.

2. The Sponsor concludes that higher amount of dronabinol can be delivered when using 1 mL of the 10 mg per capsule sesame oil formulation containing approximately 60 mg of dronabinol than 1 mL of the Oral Solution containing 5 mg of dronabinol.

3. The Sponsor did not conduct studies using concentrates of the Oral Solution (drying experiments demonstrated that the Oral solution can be concentrated to a solution containing 25 mg/mL of dronabinol), or reconstituted extracts (extraction of dronabinol from the 30 mL oral solution could produce 139-140 mg of dronabinol based on the 93 % percentage recovery extraction values reported in extraction studies).

- ***Vaporization studies using the Volcano vaporizer***

The Sponsor repeated the vaporization studies using the Volcano vaporizer. The only condition the Sponsor changed was the concentration and the amount of dronabinol in sesame oil applied to the Volcano solution holder.

Table 3 summarizes the experimental conditions used by the Sponsor in the most recent studies and in prior studies, and data from these studies. In prior studies the Sponsor had used 660 mg of the sesame oil formulation containing an equivalent amount of 10 mg or 40 mg of dronabinol depending if the sample was taken from 2.5 mg or 10 mg Dronabinol capsules (between 10 to 12 capsules). In this case 1 mL (Average weight 905.15 mg) of the sesame oil formulation collected from 7 capsule of Marinol 10 mg was used in the experiments. Current and prior studies were conducted with 1 mL of the Oral Solution. Samples were applied to the Volcano holder, heated at 230 °C (446 °F) for 25 minutes. The vapors were collected using a solvent trap containing ethanol and analyzed for THC by HPLC.

In this replication of the vaporization studies using the Volcano vaporizer, the Sponsor reported recovering an average of 0.162 mg of dronabinol (3.2 %) from the Oral solution, and on average, a recovery of 0.080 mg of dronabinol (0.1 %) from the sesame oil sample. In prior studies the Sponsor had reported a 4 % recovery of the dronabinol from the Oral solution and no recovery from the sesame oil formulation.

Reference ID: 3921488

Table 3: In Vitro Data from Vaporization Studies using the Volcano Vaporizer and by Direct Application of the Formulation to the Solution Holder, and a Vaporization Temp. 446 °F (230 °C). Highlighted cells show main differences between the experimental conditions used in prior and the most recent studies.

	Data from Studies Submitted in March, 2016		Data from Studies Submitted in January 2016	
	SYNDROS 1 mL	Dronabinol Capsules (1 mL from 7 Dronabinol 10 mg capsules)	SYNDROS 1 mL	Dronabinol Capsules 660 mg of sesame oil formulation from several Dronabinol 2.5 mg capsules
Average amount of dronabinol, in mg (% manipulation efficiency)	5 mg (100 %)	Approximately 60 mg- exact content not reported	5 mg (100%)	Approximately 10 mg- exact content not reported
Time to Visualize Vapors	3.5 min	7.5 min	6 min	No Vapors visualized
Total Vaporization Time	Dense vapors for 17 min	Faint vapors for 25 min	Faint vapors for 23 minutes	No vapors during entire process
Avg. Dronabinol recovered (mg) (% Recovered from initial sample)	0.162 mg (3.2 %)	0.080 mg (0.1 %)	0.198 mg (4.0 %)	0.003 mg (0.0 %)

***Conclusions*:**

1- The new study conducted by the Sponsor doesn't add new information; it confirms that under the conditions selected approximately between 3 and 4 % of dronabinol is recovered from the Oral solution, whereas none or 0.1 % of dronabinol is recovered from the sesame oil.

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/s/

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Division of Pediatric and Maternal Health Review

Date: April 6, 2016 **Consult Received:** June 4, 2016

From: Carol H. Kasten, MD, Medical Officer
Maternal Health Team, Division of Pediatric and Maternal Health
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Team Leader
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Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Gastroenterology and Inborn Errors Products

Drug: Syndros (dronabinol) oral solution, NDA 205-525, IND 75-228

Sponsor: Insys Therapeutics, Inc.

Indication: SYNDROS is a cannabinoid indicated in adults for treatment 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.

Consult Request: Labeling review to assure compliance with Pregnancy and Lactation Labeling Rule.

Reference ID: 3913498

INTRODUCTION

Insys Therapeutics, Inc. re-submitted this 505(b)(2) drug application for Syndros® (dronabinol) NDA 205-525 on June 1, 2015. The reference listed drug (RLD) is Marinol® (dronabinol) capsules, NDA 18-651. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2) for Syndros to assure compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

BACKGROUND

Pertinent dates for this NDA are as follows:

August 12, 2014	Initial submission of 505(b)(2) NDA
October 10, 2014	Refuse to file for failure to address Pediatric Research Equity Act, no Initial Pediatric Study Plan
June 1, 2015	Current submission

Marinol

Marinol was approved on May 31, 1985 and is currently indicated for (1) anorexia associated with weight loss in patients with AIDS; and, (2) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Marinol capsules contain dronabinol formulated in sesame oil as the drug is insoluble in water. The active pharmaceutical ingredient (API) in Marinol capsules is dronabinol, a cannabinoid that is a synthetic form of the principal psychoactive compound[1,2] in *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC). Henceforth, the term 'dronabinol' will be used when referring to the synthetic form of Δ^9-THC and when referring to the plant derived cannabinoid the term Δ^9-THC will be used.

Syndros® (dronabinol)

Syndros liquid (4.25 mg dronabinol per 0.85mL) is formulated in dehydrated alcohol. The drug is 97% protein bound and has a molecular weight of 314.46 daltons. Dronabinol has a terminal half-life of 25 to 36 hours. The labeling states that the clearance of dronabinol is highly variable due to the complex cannabinoid distribution.

Dronabinol and Δ^9-THC Mechanism of Action

Dronabinol/Δ^9-THC may bind to either of the two known cannabinoid receptors, CB1 or CB2, both of which are coupled to G-proteins and are part of the endogenous cannabinoid system (ECS).[3] Anandamide and 2-arachidonoyl glycerol are two well characterized endocannabinoid neurotransmitters in the ECS located within the central nervous system. The highest CB1 receptor concentrations identified are in the basal ganglia, cerebellum, hippocampus and cortex. CB1 receptors are also found in the ovary, uterine endometrium, testis, bladder and endocrine

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tissues.[4] In the periphery, CB2 receptors are found in the spleen, tonsils and bone marrow. Both CB_1 and CB_2 receptors are found on peripheral blood leukocytes.

When CB1receptors are activated by ligand binding, they participate in modulation of the release of neurotransmitters such as dopamine, noradrenaline, serotonin, gamma-aminobutyric acid and glutamate. It is thought that Δ^9-THC binding to CB1 receptors modulates the release of these neurotransmitters producing the drowsiness, euphoria and alteration of the senses associated with *Cannabis* inhalation.[5,6]

Neither the Marinol nor Syndros labeling elucidate the mechanism(s) by which dronabinol acts to stimulate appetite among HIV-1 infected patients. Similarly, neither labeling explains how dronabinol may reduce the symptoms of CINV.

Adverse Pregnancy Outcome Reports Associated with *Cannabis* Use

Prenatal exposure to *Cannabis* has been associated with multiple adverse pregnancy outcomes some of which are noted below.

- Gastroschisis[7,8, 9,10,11]
- Neurobehavioral abnormalities[12, 13, 14]
- Neuroblastoma[15]
- Acute Non-Lymphocytic/Myeloid Leukemia[16,17]

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[16] Robison LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC, Hammond GD: Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). Cancer 63(10):1904-1911, 1989.

[17] Trivers KF, Mertens AC, Ross JA, Steinbuch M, Olshan AF, Robison LL: Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (United States and Canada). Paediatr Perinat Epidemiol 20(2):110-118, 2006.

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- Neural tube defects[18]
- Cardiovascular malformations[19]

Each of the studies have limited exposure data regarding gestational timing, duration, quantification, concomitant medications, other illicit drug use, alcohol or tobacco use, race or ethnicity[20] and adequacy of health care. Many of the studies have very small numbers of cases or are case-control studies in which the exposure data is retrospectively collected from mothers of affected children and compared to mothers of healthy infants. With few exceptions, studies reporting adverse outcomes from prenatal *Cannabis* exposure have not been confirmed in subsequent studies.

The one malformation reported in four studies noted above is gastroschisis, an abdominal wall defect. A fifth study of a large population-based cohort, the U.S. National Birth Defects Prevention Study also found an increased risk of gastroschisis; however, this association was no longer significant once the data were adjusted for maternal age. A teratology review of the *Cannabis* exposure literature concluded that "There was a minimal risk of gastroschisis among infants of women who use marijuana during pregnancy."[21]

Another finding in many studies has been the association of prenatal *Cannabis* exposure with some form of postnatal 'behavioral alterations.'[22,23,24 25] A limitation of these reports is the postnatal environment may affect the results of the study, particularly the later the outcomes are measured. The teratology review of the literature concluded that the risk of behavioral alterations following prenatal exposure to *Cannabis* was minimal.[26]

***Cannabis* vs. Dronabinol (Δ^9-THC)**

There may be more than 400 different compounds present in the smoke from *Cannabis*.[27] Unlike

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[18] See Forrester, *et al*., 2007.
[19] See Forrester, *et al*., 2007.
[20] Pending - Childhood Cancer and association with Southwest Native American ancestry….
[21] TERIS is the TERatology Information Service located at University of Washington. Review date: December, 2011. Accessed: February 6, 2016. See Marijuana. http://www micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/
[22] See Sundram.
[23] See Huizink et al.
[24] Fried PA, Smith AM: A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. Neurotoxicol Teratol 2001;23:1-11.
[25]Fried PA: Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. J Clin Pharmacol 42(11
[26] See TERIS – marijuana.
[27] Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: July 13, 2015. Accessed: February 6, 2016.

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dronabinol, crude *Cannabis* is not regulated for purity or potency and when inhaled the total exposure of Δ^9-THC is rarely measured or reported.[28,29,30,31,32] Lapointe states,

> Marijuana is not the same entity as, nor is interchangeable with, Δ^9-THC. While the latter may be the chief psychoactive constituent of marijuana, the multiple additional cannabinoids present in marijuana are biologically active and must be considered.[33]

Some of the compounds in volatilized *Cannabis* in addition to Δ^9-THC are, cannabidiol, cannabidivarin,[34] cannabidiolic acid, cannabigerol, cannabichromene, cannabinol, Δ9-tetrahydrocannabivarin, β-caryophyllene, and tetrahydrocannibinolic acid,[35] terpenes, terpenoids[36] and fatty acid derivatives such as N-linoleoylethanolamide.[37] Not all of these compounds bind to CB1 or CB2 receptors; however, they may interact with other *Cannabis*-derived substances to potentiate and/or attenuate the effects of these compounds. The mechanisms for the combined interaction of the multiple *Cannabis* constituents are not well described. These data emphasize that *Cannabis* contains several different active compounds only one of which is found in dronabinol, the drug product to be reviewed.[38]

Dronabinol Exposure in Pregnancy and Lactation

Database Reviews

A search of the reproductive toxicology databases found no reviews of dronabinol or Marinol in Reprotox[39], Shepard's[40] or TERIS.[41] The review of dronabinol found in the LACTMED[42] database discussed data from *Cannabis* use in lactating women, not dronabinol; however, one

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[28] Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: July 13, 2015. Accessed: February 6, 2016.
[29] See Lapointe.
[30] Mello (deceased) N, Mendelson (deceased) J. Cocaine and Other Commonly Abused Drugs. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. Accessed February 6, 2016. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1130&Sectionid=79757405 .
[31] See Clinical pharmacology online.
[32] See Molinoff.
[33] Lapointe JM. Cannabinoids. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR. eds. Goldfrank's Toxicologic Emergencies, 10e. New York, NY: McGraw-Hill; 2015. http://accesspharmacy mhmedical.com/content.aspx?bookid=1163&Sectionid=65097986 . Accessed February 6, 2016.
[34] See Nikan, *et al.*
[35] See Nikan, *et al.*
[36] Terpenes and terpenoid derivatives are found throughout nature are involved in diverse biosynthetic and metabolic pathways such as cholesterol biosynthesis in humans and paclitaxel (Taxol) synthesis in the Pacific yew. (Toxline)
[37] Cascio M, Zamberletti E, *et al.*, The phytocannabinoid, Δ9-tetrahydrocannabivarin, can act through 5-HT1A receptors to produce antipsychotic effects. Brit J Pharmacol 2015;172:1305–1318.
[38] See Lapointe.
[39] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed February 6, 2016.
[40] © 2016 Shepard's: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. Accessed February 6, 2016.
[41] TERIS is the TERatology Information Service located at University of Washington. Review date December, 2011, Accessed February 6, 2016. http://www micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/

reference did demonstrate the presence of Δ^9-THC in breast milk.[43] The data from this reference will be discussed under the Literature Review.

Literature Review – Indicated Populations

One of the two indicated populations for this dronabinol review is pregnant women with chemotherapy induced nausea and vomiting (CINV) who have failed to respond to conventional antiemetic treatments. A PubMed literature search of English language publications using the terms dronabinol or Marinol and CINV yielded six references - none of which included data on pregnancy or lactation. The second indicated population for this dronabinol review is pregnant women with AIDS who have anorexia associated with weight loss. A PubMed literature search of English language publications using the terms dronabinol or Marinol and AIDS yielded 19 articles none of which included data on pregnancy or lactation.

Literature Review – Prenatal Dronabinol Exposure

A broader PubMed search for publications describing prenatal dronabinol exposure in any population was completed using the terms pregnancy or pregnant, dronabinol or Marinol yielded 74 English language articles. Two of these references provided data relevant to prenatal dronabinol exposure.

Farooq M. Ducommun E. Treatment of a hyperkinetic movement disorder during pregnancy with dronabinol. Parkinsonism and Related Disorders[44]

Only one published case report provides data on prenatal dronabinol exposure exclusively.[45] The patient in this report was a 26 year-old woman who had been treated for two years with dronabinol for a movement disorder before she became pregnant. She continued treatment with dronabinol during her pregnancy and delivered a healthy baby. No additional information was provided.

Blackard C, Tennes K. Human Placental Transfer of Cannabinoids[46]

Blood from 10 pregnant women who reported 'heavy' *Cannabis* consumption at the end of pregnancy were tested for Δ^9-THC and a metabolite, 11-nor-Δ^9-carboxy-THC (Δ^9-carboxy-THC) as was the cord blood of their newborns. Six of the 10 pregnant women and three of their newborns had measureable concentrations of Δ^9-THC in their blood or cord blood. All of the pregnant women and their newborns had measureable levels of Δ^9-carboxy-THC. Limitations of this study are (1) these data demonstrate that Δ^9-THC and its metabolite are present at birth in the newborn; however, these data provide no information on the possible presence of Δ^9-THC or its metabolite during organogenesis; and (2) the data provide no information on the maximal levels of Δ^9-THC or its metabolite that may occur at peak exposure after maternal smoking.[47]

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[42] LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 700; last revision date: 20130907, Accessed: February 6, 2016.

[43] Perez-Reyes M, Wall ME. Presence of delta 9-tetrahydrocannabinol in human milk. N Engl J Med. 1982;307:819-20. Letter. PMID: 6287261.

[44] Farooq M. Ducommun E. Treatment of a hyperkinetic movement disorder during pregnancy with dronabinol. Parkinsonism and Related Disorders 2009;15: 249e251.

[45] See Briggs.

[46] Blackard C, Tennes K. Human placental transfer of cannabinoids. N Engl J Med. 1984;311797.

[47] See Blackard.

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Literature Review – Presence of Δ^9-THC in Breast Milk

A PubMed search with dronabinol or Marinol and lactation found six references in English; one of which was a Motherisk Update on the presence of Δ^9-THC in breast milk.[48] A reference cited in the Motherisk Update is also discussed below.

Djulus J, Moretti M, Koren G. Motherisk Update - Marijuana Use and Breastfeeding.

The authors report that Δ^9-THC is a highly lipophilic substance which is rapidly distributed to the brain and body fat. The half-life of Δ^9-THC may be as long as four days and varies with the frequency of *Cannabis* exposure. Δ^9-THC is excreted in urine and feces and its presence has been detected up to a month after the last exposure. The authors concluded

- High concentrations of Δ^9-THC can accumulate in breast milk.
- A young, breastfeeding infant's brain continues to develop after birth.
- Exposure to Δ^9-THC via breast milk may affect an infant's brain development.

Perez-Reyes M, Wall ME. Presence of Δ^9-tetrahydrocannabinol in Human Milk [49]

Two lactating women who smoked *Cannabis* daily were described in this reference which used gas-liquid chromatography/mass spectrometry to measure cannabinoids in the mothers' breast milk and the urine of their infants (ages not specified). Both mothers were found to have Δ^9-THC in their breast milk. The metabolites 11–OH-Δ^9-THC and Δ^9-carboxy-THC were found in the breast milk of one mother (subject 2). Neither of the Δ^9-THC metabolites were detected in either of the infants' urine. The authors did not indicate if Δ^9-THC was present in the urine specimens. One of the breastfeeding mothers agreed to return for a second visit at which time repeat maternal blood and breast milk samples were obtained. The mother also brought with her a stool sample from her exposed infant. The results were:

Cannabinoid	**2nd Breast Milk**	**Plasma**	**Infant Stool***
Δ^9-THC	[60.3 ng/ml]	[7.2 ng/ml]	347 ng
11–OH-Δ^9-THC	[1.1 ng/ml]	[2.5 ng/ml]	67 ng
Δ^9-Carboxy-THC	[1.6 ng/ml]	[19 ng/ml]	611 ng

* Total quantities

From these data the following observations may be made:

- Δ^9-THC is present in breast milk.
- There is an eight-fold higher concentration of Δ^9-THC in breast milk relative to plasma.
- Concentrations of the two metabolites are greater in plasma than in breast milk.
- The infant stool specimen contains Δ^9-THC and the two metabolites measured.

The clinical pharmacology of all the constituents of *Cannabis* smoke are insufficiently understood to conclude that Δ^9-THC is concentrated in breast milk. The Δ^9-THC metabolites found in the infant's stool may have been directly absorbed from levels in the breastmilk, or from metabolism of Δ^9-THC in the infant. These data are extremely limited, and therefore, clear conclusions cannot be drawn.

[48] Djulus J, Moretti M, Koren G. Motherisk Update - Marijuana use and breastfeeding. Can Fam Physician. 2005;51:349-50.

[49] See Perez-Reyes.

Reference ID: 3913498

DISCUSSION

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,"[50] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[51] format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pregnancy

- 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.
- There is one publication which demonstrated that Δ^9-THC may be transported across the placenta into the fetal blood prior to delivery. This publication provides no data on placental transfer of Δ^9-THC earlier in pregnancy, particularly during organogenesis. Therefore, very limited data indicates that Δ^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 including convulsions and syncope. On this basis, DPMH recommends that pregnant women should not use dronabinol during pregnancy.

Lactation

- There are no lactation studies on the use of dronabinol in a lactating woman. There is, however, one publication which measured the concentration of Δ^9-THC and two of its metabolites, 11–OH-Δ^9-THC and Δ9-carboxy-THC, in breast milk. These data indicate that Δ^9-THC and the two metabolites are present in human breast milk and may be absorbed by the breastfeeding infant. 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.

[50] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[51] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,* published in the Federal Register (71 FR 3922; January 24, 2006).

CONCLUSIONS

- Very limited published data has demonstrated that Δ^9-THC may be transferred across the placenta and into the systemic fetal circulation. The effects of this are unknown but, given the adverse events reported with use of dronabinol in adults, use of dronabinol during pregnancy is not recommended.
- Limited published data and the pharmacologic characteristics of dronabinol (highly lipophilic, prolonged duration of storage in body fat) suggest that Δ^9-THC is present in breast milk and may be absorbed by the breastfeeding infant. Breastfeeding is not recommended while a lactating woman is being treated with dronabinol.

RECOMMENDATIONS

DPMH participated in meetings with DGIEP from July, 2015 to February 12, 2016. DPMH revised subsections (8.1) and (8.2) in the Syndros labeling for compliance with PLLR. DPMH labeling recommendations are below and reflect discussion with DGIEP on February 12, 2016. DPMH defers to the final action for Syndros for the final labeling recommendations.

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

HIGHLIGHTS

——USE IN SPECIFIC POPULATIONS——

- Lactation: Advise HIV (b) (4) infected women not to breastfeed and women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for (b) (4) days after the last dose. (8.2)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

cannabinoids have been found in the umbilical cord (b) (4) from pregnant women who smoked cannabis. In animal reproduction studies, no teratogenicity was reported in mice administered dronabinol at up to 5 times the MRHD and up to 30 times the MRHD for patients with cancer and AIDS, respectively. Similar findings were reported in pregnant rats administered dronabinol at up to 3 times the MRHD and 5 to 20 times the MRHD for patients with cancer and AIDS, respectively. Decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions were observed in both species at doses which induced maternal toxicity *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Delta-9-THC has been measured in the cord blood of some infants whose mothers reported prenatal use of cannabis, suggesting that dronabinol may cross the placenta to the fetus during pregnancy. The effects of delta-9-THC on the fetus are not known.

Animal Data

The recommended dose ranges for SYNDROS in cancer and AIDS patients are designed to achieve the same systemic exposure ranges as with the recommended dose ranges for dronabinol capsules. Therefore, animal to human dose multiples, as shown below, are based on the MRHDs (maximum recommended human doses) for dronabinol capsules, instead of the MRHDs for SYNDROS, which are 15% lower. This approach for dose comparison between animals and humans is supported by the demonstrated difference in dronabinol bioavailability between SYNDROS and dronabinol capsules.

Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m^2, equivalent to 0.2 to 5 times the MRHD of 90 mg/m^2/day (dronabinol capsules) in cancer patients or 1 to 30 times the MRHD of 15 mg/m^2/day (dronabinol capsules) in AIDS patients, and in rats at 74 to 295 mg/m^2 (equivalent to 0.8 to 3 times the MRHD of 90 mg/m^2 in cancer patients or 5 to 20 times the MRHD of 15 mg/m^2/day in AIDS patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity.

8.2 Lactation

For mothers infected with the Human Immunodeficiency Virus (HIV (b) (4)), the Centers for Disease Control and Prevention recommends not to breastfeed their infants to avoid risking postnatal transmission of HIV (b) (4). Because of the potential for HIV (b) (4) transmission in breastfed infants, advise women infected with HIV (b) (4) not to breastfeed while taking SYNDROS.

For mothers with nausea and vomiting associated with cancer chemotherapy, there are limited data on the presence of dronabinol in human milk, the effects on the breastfed infant, or the effects on milk production. The reported effects of inhaled cannabis transferred to the breastfeeding infant have been inconsistent and insufficient to establish causality. Because of the possible adverse effects from SYNDROS on the breastfeeding infant, advise women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for (b) (4) days after the final dose.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman (b) (4) SYNDROS use during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

- Advise HIV (b) (4) infected women with anorexia associated with weight loss not to breastfeed.

- Advise women with nausea and vomiting associated with cancer chemotherapy not to breastfeed during treatment with SYNDROS and for 9 days after the last dose *[see Use in Specific Populations (8.2)]*.

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/s/

CAROL H KASTEN
04/06/2016

TAMARA N JOHNSON
04/07/2016

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04/11/2016

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M E M O R A N D U M

From: Erica Radden, M.D.
Division of Pediatric and Maternal Health,
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Through: Donna Snyder, M.D., Acting Pediatrics Team Leader,
John Alexander, M.D., M.P.H., Acting Deputy Director,
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Syndros (dronabinol) Oral Solution

Application number: NDA 205525 (IND 75228)

Re: Labeling review for new formulation

Applicant: Insys Therapeutics, Inc.

Proposed Indications: In adults:

- 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

Proposed Dosage form and Route of administration: Oral solution: 150 mg/30 mL (4.25 mg/0.85 mL)

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Proposed Dosing Regimen:

Anorexia Associated with Weight Loss in Adult Patient with AIDS:

- [redacted] (b) (4) (2.125 mg) orally twice daily, one hour before lunch and supper.

Nausea and Vomiting Associated with Chemotherapy in Adult Patients Who Failed Conventional Antiemetics:

- Starting dose of [redacted] (b) (4) (4.25 mg/m^2), administered 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. [redacted] (b) (4)

Consult Request: DGIEP requested DPMH's assessment of the acceptability of this application for filing with regards to PREA requirements and assistance with preparation for the Pediatric Review Committee meeting.

Materials Reviewed:

- Applicant's proposed labeling for Syndros (dronabinol) oral solution (January 15, 2016)
- Current Marinol (dronabinol) capsules labeling (June 21, 2006)
- Prior DPMH consult review on Dronabinol, NDA 205525 (October 10, 2014)
- Pediatric Review Committee minutes from the February 3, 2016 meeting (dated February 18, 2016 in DARRTS)
- Office of Surveillance and Epidemiology (OSE) Drug Utilization Review (March 15, 2016)

Background:

On August 12, 2014, Insys Therapeutics, Inc. (Insys) submitted a 505(b)(2) new drug application for Syndros (dronabinol) oral solution, relying on FDA's findings of safety and effectiveness for Marinol (dronabinol) capsules as the reference listed drug. Dronabinol contains an orally active synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Marinol capsules are approved for both the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who failed to respond adequately to conventional antiemetic treatments, and for anorexia associated with weight loss in patients with AIDS. Labeling for Marinol states that use "is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population." Marinol labeling also states that "the pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults", implying a pediatric indication. Insys (the applicant for Syndros) seeks the same indications for Syndros, but only in adults. Of note, the proposed Syndros oral solution contains the excipients dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w).

Prior to the submission of their NDA in August, 2014, Syndros failed to submit an initial Pediatric Study Plan (iPSP). In their submission, Insys included a pediatric plan requesting a [redacted] (b) (4)

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(b) (4). Inadequate data was provided to support their request, and a Refuse to File letter was issued on October 10, 2014. Subsequently, Insys submitted an iPSP on November 3, 2014, which was negotiated with the Agency. Ultimately, an agreed iPSP letter was issued on May 20, 2015 which outlined the following:

- For anorexia associated with weight loss in patients with AIDS:
  - A partial waiver for patients 0-14 years of age because necessary studies are impossible or highly impracticable due to the low incidence in this population
  - (b) (4) trial in patients 15-17 years of age.
- For treatment of nausea and vomiting associated with cancer chemotherapy:
  - A (b) (4) PK/PD trial in pediatric cancer patients 0-17 years of age
  - (b) (4) tolerability, and efficacy study in pediatric cancer patients 0-17 years of age

Of note, Insys is (b) (4) to conduct their pediatric studies.

DGIEP has requested DPMH's assistance with the review of this application and labeling of pregnancy, lactation and pediatrics.

Comments on PREA and Pediatric Study Requirements:
Under PREA, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The proposed efficacy supplement triggers PREA as a new dosage form.

Insys submitted a pediatric plan that was unchanged from the proposed waivers and studies outlined in the agreed iPSP noted above. Syndros' pediatric plan was discussed at the Pediatric Review Committee meeting on February 3, 2016. No new data was provided since the previously agreed upon iPSP, but one member noted concern that based on recently published data, the prevalence of AIDS in adolescents is very low, and a study evaluating AIDS-related anorexia in patients 15-17 years of age would be infeasible. DGIEP noted, however, that the applicant had agreed to conduct this study based on the epidemiologic data that was provided by the applicant. After considerable discussion, PeRC was split on the pediatric plan for AIDS-related anorexia indication, voting 5-4 in favor of a full waiver of pediatric studies for this indication. Nevertheless, PeRC deferred the final decision to DGIEP. The PeRC agreed to the plan for studies of CINV in patients 0-17 years of age.

DGIEP also consulted OSE to conduct a drug utilization review to provide data on the use of dronabinol in the pediatric population to further inform their decision on pediatric

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study requirements. The review found that although use was relatively low in the pediatric population (1%-2% annually of total number of patients receiving a dispensed prescription for dronabinol in the outpatient setting from 2006 through 2015), pediatric utilization had more than doubled over the review period in both patients 0-14 and 15-17 years of age. By 2015, of the 1,700 pediatric patients who received a dispensed prescription for dronabinol in the outpatient retail pharmacy setting, approximately 1,000 pediatric patients were aged 0-14 years, and approximately 700 pediatric patients were aged 15-17 years. However, due to the low pediatric utilization of dronabinol in the outpatient setting, the office-based physician's survey results did not capture any data associated with the use of dronabinol for anorexia among pediatric patients 15-17 years old. Additionally, no diagnoses associated with the use of dronabinol were reported for pediatric patients 0-14 years old for the review period. Because use of dronabinol for AIDS-related anorexia in the pediatric population is off-label, the limited data that was captured can rule in current use, but not necessarily rule out potential use. Nevertheless, DPMH agrees that studies in patients 15-17 years for AIDS-related anorexia would be extremely challenging due to the low prevalence of the condition in this population and would support a waiver for this indication if DGIEP determined studies were not feasible.

DPMH Review of labeling:
The DPMH- Pediatrics team labeling review will focus on edits to sections (b) (4) 5 (Warnings and Precautions), and 8.4 (Pediatric Use).

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, all relevant pediatric information related to the unapproved use should be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. The guidance also states that any negative or inconclusive pediatric studies must be described in the Pediatric Use subsection, and the basis for the determination of safety and effectiveness in the pediatric population should also be provided (e.g., providing an explanation for why the available evidence does not support pediatric approval). (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

Discussion on Pediatric Use Labeling Recommendations:
SYNDROS contains the excipients dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). The applicant proposes to include (b) (4)

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(b) (4)

juvenile animal studies with Syndros have not yet been conducted. Furthermore, the association of this finding specifically with dronabinol, is unclear and the data would need to be reviewed by the Agency. Therefore, sufficient data are not available at this time to support (b) (4) should be excluded. A determination regarding the (b) (4) can be revisited if juvenile animal data for Syndros suggests a potential safety concern.

Because Marinol capsules are labeled in pediatric patients for CINV and the proposed oral solution for Syndros is more pediatric-friendly, off-label use is anticipated and labeling should reflect safety concerns associated with use in the pediatric population. Regarding the Warnings and Precautions section, labeling should reflect the potential for increased sensitivity to the neurological and psychoactive effects of SYNDROS in pediatric patients with a cross-reference to the Pediatric Use section (8.4). Additionally, when administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. This interaction is of particular concern in neonates who have a diminished ability to metabolize propylene glycol and are more susceptible to propylene-glycol related toxicities including: hyperosmolarity (with or without lactic acidosis), renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias, and electrocardiogram (ECG) changes, and hemolysis. A warning regarding this concern for toxicity in preterm infants should be included in section 5, with the caveat that safety and effectiveness of Syndros have not been established in pediatric patients. Lastly, subsection 8.4 should briefly describe the concern for neurological and psychoactive effects of Syndros in pediatric patients and the concern for toxicity in preterm infants with a cross-reference to the related areas of labeling in section 5. Because Syndros will not be approved for pediatric use, subsection 8.4 should also state that safety and effectiveness of Syndros have not been established in pediatric patients.

See Appendix 1 for Applicant's Relevant Proposed Labeling for Syndros

DPMH Recommended labeling for Syndros:

5.4 Neurological Adverse Reactions

Cognitive Adverse Reactions

Use of SYNDROS has been associated with cognitive impairment and altered mental state. Reduce the dose of SYNDROS or discontinue use of SYNDROS if signs or symptoms of cognitive impairment develop. Elderly and pediatric patients may be more sensitive to the neurological and psychoactive effects of SYNDROS *[see Use in Specific Populations (8.4), (8.5)]*.

Reference ID: 3910865

5.7 Toxicity in Preterm Neonates

SYNDROS contains the excipients dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby, leading to accumulation (b) (4).

The safety and effectiveness of SYNDROS has not been established in pediatric patients. (b) (4) SYNDROS in preterm neonates in the immediate postnatal period because of possible toxicities including: hyperosmolarity, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias, and electrocardiogram (ECG) changes, and hemolysis.

8.4 Pediatric Use

The safety and effectiveness of SYNDROS have not been established in pediatric patients.

Pediatric patients may be more sensitive to neurological and psychoactive effects of SYNDROS. SYNDROS contains the excipients 50% (w/w) dehydrated alcohol and 5/5% (w/w) propylene glycol. (b) (4) ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation (b) (4) *[see Warnings and Precautions (5.4, 5.7)]*.

Conclusion:
DPMH agrees that pediatric studies for the AIDS-related anorexia indication would be very challenging to conduct in patients 15-17 years of age and may not be feasible. DPMH agrees with the pediatric study requirements for patients 0-17 years of age for the CINV indication.

DPMH provided recommendations on the description the negative trial in the Pediatric Use subsection of labeling per 21 CFR 201.57(c)(9)(iv). DPMH reviewed the applicant's draft labeling, and participated in the team and labeling meetings held between November, 2015 and March, 2016. DPMH will continue to participate in the upcoming team meetings and application review. The above recommendations were provided to DGIEP. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

Reference ID: 3910865

Appendix 1: Applicant's Relevant Proposed Labeling for Syndros

(b) (4)

8.4 Pediatric Use

The safety and effectiveness of SYNDROS have not been established in pediatric patients. (b) (4)

(b) (4)

psychoactive effects.

Reference ID: 3910865

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/s/

ERICA D RADDEN
04/01/2016

DONNA L SNYDER
04/01/2016

JOHN J ALEXANDER
04/01/2016

Consult Memo: ICC1500288/ NDA 205525

Addendum to Review Memo

Date:	March 21, 2016
From:	Sarah Mollo, DAGRID/GHDB
To:	Kathlene Fitzgerald, Lead Reviewer, DAGRID/GHDB
Type of Product:	press in bottle adaptor and oral syringe
Product Name:	Drobinol oral solution
Intended Use:	administration of drobinol oral solution
Sponsor:	Insys Therapeutics, Inc
Consult Review:	Biocompatibility of the Device Constituent

I. Scope of Consult

This consult is a review of the biocompatibility of the patient and fluid contacting components of the press in bottle adaptor and oral syringe.

II. Documents Reviewed

IR Response Toxicity Evaluation Report (b) (4)-SR025A
IR Response Leachable Project Report (b) (4)-M0075
IR Response Leachable Project Report (b) (4)-M0075
Response to Mid Cycle Information Request
IR Response e_1 Summary Memo - November 12, 2015
Response to Filling Review Issues – Device
IR response oral-solution-disp-dev description
Response to IR_(b) (4)
Proposed labeling
Device Description - Dronabinol Oral Solution Dispensing
15t-67759-02-(b) (4)-dispenser
15t-67759-03-15t-67759-04-(b) (4)-dispenser
15t-67759-05-15t-67759-06-(b) (4)-dispenser
15t-67937-02-(b) (4)-adaptor
15t-67937-03-15t-67937-04-(b) (4)-adaptor
15t-67937-05-15t-67937-06-(b) (4)-adaptor
(b) (4)-mid-cycle-info-req

III. Addendum to Review added on March 21, 2016

On March 18, 2016, the sponsor submitted information to demonstrate that the only change in the syringe is on the barrel graduation markings per DMEPA's request: "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."

The sponsor has stated the following:

"The (b) (4) *and* (b) (4)*, and corresponding* (b) (4) *and* (b) (4) *listed above, used for the Barrel and Plunger for the 41-0008-163 dispenser are identical to the Barrel and Plunger of the 41-0236-001 dispenser that is currently under review under the NDA 205525 in formulation and processing and no other chemicals have been added in our process. (e.g.,* (b) (4) *etc.).* (b) (4) *."*

Additionally, they sponsor has provided a comparison table of the raw material used in the to-be marketed syringe and the syringe that was reviewed in this memo under NDA 205525.

Raw Material	(b) (4) Part # 41-0236-001	(b) (4) Part # 41-0008-163
		(b) (4)

Reviewer Comment
The sponsor was stated that to-be marketed syringe and the syringe that syringe that was reviewed under the NDA 205525 are identical in material formulation and processing. The biocompatibility and drug compatibility testing that has been performed on the syringe that we reviewed under NDA205525 (41-0236-001) can be leveraged for the evaluation of the proposed to-be marketed syringe (41-0008-163).

IV. Review Summary

All deficiencies have been resolved through interactive review. The sponsor has provided all requested information and test reports. The information within the submission and supplements was adequate to perform a biological evaluation of the devices. The consulting reviewer does not believe that use of the device will result in a toxicological response.

V. Background

Dronabinol Oral Solution is a new formulation of dronabinol intended for oral delivery. Dronabinol Oral Solution contains a synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Dronabinol is an orally active cannabinoid that has many effects on the central nervous system, including sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues and may play a role in mediating the effects of dronabinol and other cannabinoids.

Dronabinol Oral Solution has the same active ingredient, dronabinol, as Marinol® oral capsule and generic dronabinol oral capsule formulations. Inactive ingredients are butylated hydroxyanisole, sucralose, methyl paraben, propyl paraben, dehydrated alcohol (50% w/w), polyethylene glycol400, and propylene glycol.

Dronabinol Oral Solution is packaged in a 30 mL container containing 150 mg dronabinol (5 mg/mL). Dronabinol Oral Solution is co-packaged with an oral dosing syringe marked with the graduations allowing the measurement of prescribed doses.

Proposed Clinical Use

Dronabinol Oral Solution is indicated for the treatment of:
1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in

APPEARS THIS WAY ON ORIGINAL

Indications for use: For the treatment nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.

This product, which was developed under IND 75228 is packaged in a 30 mL container, which is copackaged with a dispenser for oral administration.

VI. Device Description

Oral Dispenser

A clear graduated oral dispenser is provided along with the bottle and press-in bottle adapter for use by the patient in dispensing the product. The oral dispenser will allow the patient to draw the desired dose with accuracy.

The dispenser consists of two parts, a Barrel and a Plunger. The graduation scale is printed on the barrel with a black printing ink. The list of components of the oral dispenser is provided hereafter:

- Barrel:
  - (b) (4)
  - o
  - o
- Plunger:
  - (b) (4)
  - o
  - o

Press-In Bottle Adaptor

A Clear vented 20 mm press-in bottle adapter is provided along with the oral dispenser for dispensing Dronabinol Oral Solution from the bottle. At the time of first use, a press-in bottle adapter is fitted on to the bottle and kept there for the entire duration of use. The press-in bottle adapter allows a user to easily draw liquid with the oral dispenser, ensuring accurate dosing while avoiding spills. The adapter fits with the bottle opening so that the original cap can be placed on the bottle. The press-in bottle adapter is manufactured from (b) (4). For commercialization, the press-in bottle adapters are wrapped individually in plastic film.

VII. Biocompatibility Review History

The following IRs were sent as part of the "Filing Communication - Filling Review Issues Identified" letter dated August 12, 2015:

FDA Question 9
You stated you performed a chemical stability study in which the dronabinol oral solution was held in the dispensing syringe for 8 hours and the impurity levels were assessed (table 1 on pg. 3 of 3.2.R.4). Provide the data for the leached substances for this test. Alternatively, clarify the use-life of the syringe (i.e., how many times the syringe will be reused and/or over what period of time) and perform a risk assessment the leachables after an incubation period with the drug, consistent with the use-life.

> ***Insys Response***
> *An extractable study was performed using the oral dispensing syringe using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the syringe components for 24 hours (Extractable Report referenced (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose of (b) (4) mL, an analytical evaluation threshold (AET) and reporting threshold were calculated for the amount of extractable per device.*
>
> *Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds based on allowable maximum dose of (b) (4) mL (Table 1). Toxicological evaluation showed that PDE for all the compounds th*at can possibly be extracted under reflux conditions were below the acceptable daily intake (ADI) level (Toxicity Evaluation Report (b) (4)-SR025A, Table 2 and Summary Memo dated November 12, 2015).

FDA Question 10
The directions for use state that the opened bottle can be stored for up to 28 days; however, it is unclear if the adapter will be re-used in subsequent bottles of dronabinol oral solution. Clarify the use-life of the adapter and provide leachables/extractables testing using dronabinol as the solvent for the adapter according to the use-life conditions. Alternatively, you can use accelerated conditions (i.e. 50◦ C for 72 hours) to assess the possible leachants/extractants resulting from the interaction between the drug and the adapter.

> ***Insys Response***
> *It is not recommended to re-use the adapter in subsequent bottles of Dronabinol Oral Solution. For each new prescription a new unit of use container is delivered to the patient. The unit of use container includes a 30mL light-resistant bottle containing 150mg of Dronabinol (4.25 mg / 0.85 mL), an oral syringe, and an adapter. It is clearly indicated on the carton submitted in this sequence that the product should be dispensed in this unit-of use container.*

An extractable study was performed using the press-in bottle adapter using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the bottle adapter for 24 hours (Extractable Report (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose an analytical evaluation threshold (AET) and reporting threshold was calculated for the amount of extractable per device.

Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds. Toxicological evaluation showed that PDE for all the compounds that can possibly be extracted under reflux conditions was below the acceptable daily intake (ADI) level. Refer to Toxicity Evaluation Report (b) (4)-SR025A, Table 1, Table 2 and Summary Memo dated November 12, 2015 for detailed information.

The targets for leachables were identified based on the extractable characterization study. The leachables analysis was performed on drug product sample that was held in the presence of bottle adapter for 28 days at ambient conditions. The bottle was placed in horizontal orientation to provide constant contact of bottle adapter with drug product solution. None of the potential leachables were detected in this sample (Leachable Report (b) (4)-M0075). Based on the results of leachable study the bottle adapter can be in contact with the drug product during its use over 28 days at ambient conditions of storage.

FDA Question 11

You provided an USP <661> testing summary for the syringe barrel and plunger as well as the bottle adapter; however, the information in this summary was limited. Provide your test protocol(s), including but not limited to the specific solvents used, extraction time, extraction ratio and extraction conditions. Provide an evaluation of your results including an explanation as to why the amount (mg) of nonvolatiles extracted does not present a safety concern to the patient.

Insys Response

In the previous response dated August 28, 2015, Insys provided experimental details of USP <661> testing. This is a gravimetric test and the limits have been developed by USP in order to assess suitability of material being used in the manufacture of components used.

For the evaluation of safety of any leachables that may be present due to exposure to syringe and bottle adapter, Insys conducted extractable characterization and leachable identification studies as outlined in response to Questions 9 and 10. A leachables study showed that only one compound (b) (4) was observed above the analytical evaluation threshold for the syringe sample and the amount present is well below the acceptable daily intake. The bottle adapter did not show any leachables present above AET. Based on this analysis leachables expected to be present due to syringe and bottle adapter contact are well below any toxicity concern.

The following IRs were sent as part of the Mid Cycle Information Request letter dated November 17, 2015:

FDA Question 1

The information describing the nature and duration of patient contact of the oral dispenser and press-in adapter device components could not be located within the submission. Please provide a description of the category and duration of contact of each device component (i.e. adapter and syringe).

Insys Response
Category of the device is Surface Device. Based on the review of the tapes of the label comprehension study submitted on June 01, 2015, the total amount of time spent contacting the adapter or syringe was approximately five minutes. Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h). Please refer to the report of the label comprehension study, submitted on June 01, 2015, for details on this study.

FDA Question 2
Additionally, we were unable to locate an evaluation of the biocompatibility of the oral dispenser and press-in adapter device components. Please provide the appropriate biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. Please provide the test summaries, test method (including sample preparation and acceptance criteria), full test reports, and an analysis of the results.

Insys Response
Please find the accompanying letter from the manufacturer of the adapters and syringes attesting these products are currently being used for OTC, Rx, and Oral Liquid applications. They are Class I Medical Devices and are exempt from 510K Pre-Market Submission requirements. The manufacturer, (b) (4) has provided USP Class VI testing for the (b) (4) used in the manufacture of barrel for oral dispenser.

As Dronabinol Oral Solution is now classified as a combination product, Insys will initiated the biocompatibility study with the oral dispenser and bottle adapter and anticipate submission of results to FDA by middle of January 2016.

Updated Insys Response
In response to this question, Insys initiated biocompatibility studies with the oral dispenser and bottle adapter.

Based on the FDA draft guidance, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" issued on April 23, 2013, the oral dispenser and adapter are both classified as surface devices and have limited contact. Biocompatibility testing needed are Cytotoxicity, Sensitization, and Intracutaneous Reactivity. These tests were performed by contract testing lab (b) (4) under pre-approved protocols and results are summarized below. Devices meet the requirement of biocompatibility as defined in the guidance. Please note, section 3.2.R.4 was updated to describe biocompatibility study results as well.

1) Cytotoxicity: The test articles, Oral Dispenser and Adapter, were evaluated separately for potential cytotoxic effects using an in vitro mammalian cell culture test. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A single preparation of the test article was extracted in single strength Minimum Essential Medium (lX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly extracted. Triplicate mono layers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% C02

for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration. The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test because the grade was less than a grade 2 (mild reactivity). Details of the methodology followed and test results are in the attached reports 15T_67759_02 (dispenser) and 15T_67937_02 (adaptor).

2) Sensitization: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices -Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test. Details of the methodology followed and test results are in the attached reports 15T_67759_05/15T_67759_06 (dispenser) and 15T_67937_05/15T_67937_06 (adaptor).

3) Intracutaneous Reactivity: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively. Details of the methodology followed and test results are in the attached reports 15T_67759_03/15T_67759_04 (dispenser) and 15T_67937_03/15T_67937_04

VIII. Biocompatibility Summary

The following response was provided by the sponsor for duration of patient contact:

Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h).

The oral syringe and press in bottle adaptor will come into contact with patient skin (limited contact). However, the device will also come into contact with the drug, which will then be administered orally. Therefore, the sponsor was requested to perform a chemical characterization and risk assessment to address the systemic toxicity of possible leachables from the device.

Biocompatibility testing provided by the sponsor

The sponsor conducted the following biocompatibility testing on the oral syringe and press-in bottle adaptor:

a. *In vitro* cytotoxicity
b. Sensitization;
c. Intracutaneous reactivity;

The biocompatibility testing was conducted by [redacted] declared that the biocompatibility testing was conducted in accordance with 21 CFR Part 58. The extraction conditions and test methods were performed in accordance with 10993-5 and 10993-10. The results demonstrated that the devices were: non-cytotoxic, non-sensitizing, and non-irritating.

Extractables and leachables Studies

Extractable Report Summary

The samples were characterized for volatile, semi-volatile, and non-volatile/polar organic extractables and inorganic extractables. Volatile compounds and [redacted] were characterized using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionization (EI), and semi-volatile compounds were characterized using gas chromatography-mass spectrometry (GC-MS) with EI. Nonvolatile/ polar compounds were characterized using high performance liquid chromatography-ultraviolet-mass spectrometry (HPLC-UV-MS) with positive and negative atmospheric pressure chemical ionization (APCI). Inorganic compounds were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS).

Volatile compounds were analyzed directly by HS GC-MS from the headspace of the samples in sealed vials incubated at an elevated temperature. Semi-volatile and nonvolatile/ polar extractables were generated for the adapter, barrel, and plunger components by 24-hour reflux extraction of the samples in 50:50 water:ethanol (H2O:ethanol) and isopropanol (IPA). The IPA extracts were not semi-quantitated [redacted] were only generated to aid in the peak identification for the extracts which do mimic the drug product.

Inorganic extractables were generated for the adapter, barrel, and plunger by maceration in dilute nitric acid for 24 hours at 60 °C. The semi-volatile extractables were profiled by GC-MS, and non-volatile/polar extractables were analyzed by HPLCUV-MS. The inorganic extractables were analyzed by ICP-MS. The reporting threshold was [redacted]ppm for the HS GC-MS analysis, and the Analytical Evaluation Threshold (AET) was applied in the GC-MS, HPLC-UV-MS, and ICP-MS analyses.

In the HS GC-MS analysis, [redacted] were observed above the reporting threshold for the adapter, barrel, and plunger samples. [redacted] were also observed above [redacted]ppm for the barrel sample.

In the GC-MS analysis, [redacted] were observed above the AET for the barrel 50:50 H2O:ethanol extract. No peaks were observed above the AET for the adapter and the plunger extracts.

In the LC-MS analysis, (b) (4) was observed above the AET or the barrel 50:50 H2O:ethanol extract. No peaks were observed above the AET for the adapter and the plunger extracts.

Leachables Report Summary

(b) (4) *conducted an in-use leachables assessment for Dronabinol Oral Solution drug product in contact with transient container systems consisting of a press-in bottle adapter and dispensing syringe for Insys Therapeutics (Customer). The migration study was conducted for 28 days at room temperature for the press-in bottle adapter and for 8 hours at room temperature for the syringe.*

The samples were screened for volatile, semi-volatile, and non-volatile organic leachables and inorganic leachables. Volatile compounds and (b) (4) *were characterized using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionization (EI), and semi-volatile compounds were characterized using gas chromatography-mass spectrometry (GC-MS) with EI. Non-volatile/polar compounds were identified using high performance liquid chromatography-ultraviolet-mass spectrometry (HPLC-UV-MS) with positive and negative atmospheric pressure chemical ionization (APCI). Inorganic compounds were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS).*

Volatile leachables were prepared by combining the drug product with methanol to adulterate the product. Semi-volatile and non-volatile/polar leachables were prepared by liquid-liquid extraction of the drug product with methylene chloride. Inorganic leachables were prepared by microwave extraction in a concentrated hydrochloric acid and 30% hydrogen peroxide mixture. The Analytical Evaluation Threshold (AET) was applied in the HS GC-MS, GC-MS, HPLC-UV-MS, and ICP-MS analyses.

For the HS GC-MS analysis, no non-control related peaks were observed above the AET for the adapter and syringe migration samples.

For the GC-MS analysis, (b) (4) *was observed above the AET in the syringe migration sample. No peaks were observed above the reporting threshold in the adapter migration sample.*

No non-control related peaks were observed above the reporting threshold for the migration samples, for the HPLC-UV-MS analysis.

For the metals analysis, no elements were observed above the reporting threshold for the migration samples.

A spiking study was conducted for all analyses to determine if compound classes commonly observed in plastics could be observed by the screening methods in the presence of the drug product matrix at the AET concentration. All targets were observed by all screening methods with the exception of (b) (4) *by HS GC-MS analysis.*

Reviewer Comment

The extraction methods used for the extractables and leachables studies are acceptable. The leachable migration study of 28 days for adaptor; and the 8 hours for the syringe is consistent with conditions of use. Use of 50:50 water:ethanol (H2O:ethanol) and isopropanol (IPA) as solvents is acceptable. The IPA extracts were not semi-quantitated (b) (4) were only generated to aid in the peak identification for the extracts which do mimic the drug product.

Quantitation of the 50:50 ethanol water solvent only is acceptable, as the sponsor states that is representative of the Dronabinol Oral Solution formulation.

The analytical chemistry approach used to identify and quantify extractables appears to be appropriate. A number of extractable compounds were identified and the ADI value for each of the extractables present over the AET was calculated correctly by the sponsor either from toxicity data in the literature or by the use of the TTC approach (see below for a summary of the toxicological risk assessment).

Toxicological Risk Assessment

The extractables specified in Table 1 below were identified as potential leachables of a pharmaceutical drug product. Table 1 provides the Potential Daily Exposure (PDE) to these extractables with clinical use of the inhalation drug product. Table 1 also indicates the number of times the Acceptable Daily Intake (ADI) or Threshold of Toxicological Concern (TTC) exceeds the PDE for adults (60-kg mean bw) and children (11-kg mean bw), and the associated human health risk assessment (safe or unsafe) for each specified extractable. The risk assessment referenced the data/resports used to develop the ADI or TTC values and summarized this information in tables 3a and 3b.

If possible, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) approach was used to compute an ADI based on uncertainty factor (UF) multiples of 10 and mean body weight (bw). The calculated ADI is then compared to the PDE to estimate the human health risk. TTC values are established as needed *via* Toxtree, for estimation of toxicity using a decision tree approach. The TTC approach is applied for cases where a reliable ADI cannot be established from relevant scientific literature. The specified extractables of the inhalation drug product have been determined to be safe for human exposure during clinical use of the product, based on the specified PDEs.

The ratios of ADI/PDE (or TTC/PDE) for the extractables range from (b) (4) and from (b) (4) for adults and children, respectively. The term "safe" is applied whenever the PDE is below the ADI or TTC (the ADI/PDE or TTC/PDE ratio >1). The ratios of ADI/PDE or TTC/ADI are representative of margins of human safety. Determination of safety where ADI/PDE or TTC/PDE ratios < 1 are made on a case-by-case basis. See footnote to Table 1.

The reference dose (RfD in mg/kg bw/day) is defined as an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of significant health effects during a lifetime. The RfD is determined by use of the following equation: RfD = (NOAEL or LOAEL)/(UF), where the NOAEL is the "no observed adverse effect level" and LOAEL is the "lowest observed adverse effect level". UF is called the uncertainty factor. UFs are products of 10 that are used to lower the NOAEL or LOAEL due to uncertainty in the critical study used to determine the LOAEL or NOAEL. The following criteria are used to calculate UFs:

(i.) Use one factor of ten to account for the variation in sensitivity to the chemical among members of the human population.
(ii.) Use one factor of ten to account for the uncertainty of extrapolating data from animal studies to humans.
(iii.) Use one factor of ten to account for use of data from a subchronic study (less than 90 days).
(iv.) Use one factor of ten when the LOAEL is used instead of the NOAEL.

Acceptable daily intake (ADI) is calculated from the Reference Dose (RfD)
For adults: ADI (mg/day) = (RfD in mg/kg bw/day) x 60-kg mean Body Weight
For children: ADI (mg/day) = (RfD in mg/kg bw/day) x 11-kg mean Body Weight

Reviewer comment
The uncertainty factors used by the sponsor were conservative. The method used to calculate the ADI is acceptable.

Table 1. Extractable, CAS Number, Acceptable Daily Intake (ADI), Potential Daily Exposure (PDE), the number of times the Acceptable Daily Intake (ADI) or Threshold of Toxicological Concern (TTC) exceeds the PDE for adults (60-kg bw) and children (11-kg bw), and the Human Safety Assessment.

Extractable	CAS No.	ADI or TTC [1] [µg/day]	PDE [µg/day]	ADI/PDE [2] or TTC/PDE	Human Safety Assessment
(b) (4)					Safe
					Safe
					Safe
					Safe
					Safe

(b) (4)	
	See comment below*
	Safe
	Safe
	Safe
	Safe

[1] Values in this column are for ADIs unless otherwise noted.

[2] Refer to Tables 2, 3a and 3b for details.

(b) (4)

Reviewer Comment

In most cases, the calculated ADI values of the compounds extracted from the device are well above the estimated daily exposure values for the compounds, yielding Margin of Safety (MOS) values >1. However, the MOS for one compound, (b) (4) (see table below).

(b) (4)

The ADI calculated for this compound is based on NOAEL of (b) (4) mg/kg/day and a modifying factor of 1000, with factors of 10 each used to account for inter-individual variability, interspecies differences in potency, and the use of a NOAEL from a short-term toxicity study. Since use of the drug product is not likely to occur over a lifetime, the use of the UF of 10 for short-term toxicity data yields a modifying factor (MF) of 1000 (10 x 10 x 10) that is probably overly conservative for this device. An alternate approach would be to base the MF simply on the product of the UFs to account for inter-individual variability (10) and interspecies differences in potency (10), resulting in a MF of 100 and an ADI of (b) (4) mg/kg/day or (b) (4) µg/day for a 60 kg adult and (b) (4) µg/day for a 10 kg child. Both of these ADI values are greater than the dose of the compound extracted from the device, resulting in a MOS > 1.

Reviewer comment

The ADI values for each of the compounds were derived using data from noncancer endpoints in toxicity studies or TTC values intended to be protective for noncancer endpoints. The ADI values used in the risk

assessment were derive ADI values that are protective for noncancer and cancer-based effects. Dr. Ronald Brown (toxicologist, OCEL) provided the following rationale for the acceptability of this approach:

The ADI values for each of the compounds were derived using data from noncancer endpoints in toxicity studies or TTC values intended to be protective for noncancer endpoints. However, if the device can be used for a prolonged period, then it is important to derive TI values that are protective for both cancer-based and noncancer effects. Screening of the extractables for potential carcinogenicity using the Toxtree program resulted in identification of two compounds with structural alerts for genotoxic carcinogenicity and mutagenicity in the Ames test, (b) (4). A search of the CCRIS database reveals that (b) (4) has been tested in several strains of *S. typhimurium* in the Ames test and the results negative. (b) (4) has been tested in multiple genotoxicity test systems and has shown negative results in the Ames test, *in vitro* micronucleus, *in vitro* chromosomal aberrations, and unscheduled DNA synthesis, but positive results when tested in CHO V79 cells. Although positive results were reported in this assay, this compound has undergone extensive *in vitro* genotoxicity testing in a battery of assays and the weight of evidence suggests that the compounds is not genotoxic. Therefore, despite the presence of a structural alert for carcinogenicity and mutagenicity, the (b) (4) compounds extracted from the device are not likely to be genotoxic. Consequently, the ADI values used by the submitter in the risk assessment are appropriate. Since none of the compounds extracted from the device are likely to be mutagenic, no additional genotoxicity testing is needed to assess the carcinogenic potential of extractables released from the device.

Reviewer Comment
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.

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

/s/

MAUREEN D DEWEY
03/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 23, 2016
From: Kathleen FitzGerald, Nurse consultant WO66, RM2510
CDRH/ODE/DAGRID/GHDB
To: Maureen Dewey CDER/OND/ODEIII/DGIEP
Subject: ICC1500288, CDRH/ODE Oral Dispenser and Press-In Adapter device components review for NDA 205525 Dronabinol Oral Solution

1. Issue/Request from CDER:
The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding the oral syringe in NDA 205525 Dronabinol Oral Solution.
This product, which was developed under IND 75228 is packaged in a 30 mL container, which is copackaged with a dispenser for oral administration.
This is being filed as a 505(b)(2) application with NDA 018651 for Marinol® (dronabinol) capsules as the reference drug. Dronabinol Oral Solution is indicated for the (b) (4) nausea and vomiting associated with cancer chemotherapy (b) (4).
Please provide expertise on all matters related to manufacturing aspects of syringes and Human Factor studies.
This submission can be accessed through the following link:
\CDSESUB1\evsprod\NDA205525\205525.enx

This review is limited to the oral dispenser and press-in adapter used in NDA 205525.

CDER is reviewing the primary container 30 mL clear amber color (b) (4) glass bottle that contains Dronabinol Oral Solution. The bottle closure is a 20 mm child-resistant cap with a Teflon coated liner.

DMEPA will be reviewing the Human Factors portion.

Sarah Mollo, CDRH/ODE/GHDB, reviewed the biocompatibility data and test reports for the Oral Dispenser and Press-In Adapter.

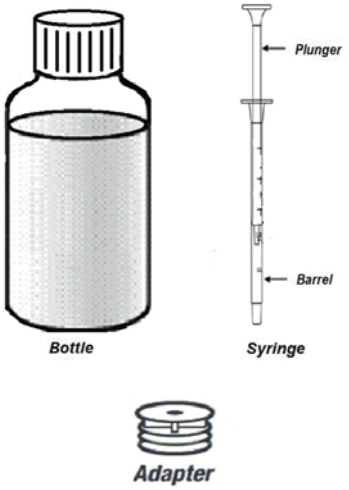
2. **Device Description:**
Product Name: Dronabinol Oral Solution

Reference ID: 3907554

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.

Container Closure System Description:
Dronabinol Oral Solution is packaged in a multi-dose container closure system. Standard pharmaceutical packaging materials were selected for the product.
The primary container is 30 mL clear amber color (b) (4) glass bottle. The bottle closure is a 20 mm child-resistant cap with a Teflon coated liner.
Refer to Section 3.2.P.7.1 for detailed technical and regulatory information for the bottle and child-resistant cap including materials of construction, drawings and controls.
The container is wrapped with a PVC body band to provide tamper evidence and packaged in a suitably sized carton along with a graduated oral dispenser.

A clear graduated oral dispenser and press-in bottle adapter are provided in the carton along with drug product and package insert. At the time of first use, the press-in bottle adapter is fitted on to the bottle that allows the patient to draw the product using an oral dispenser with ease.
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 clinical trial INS-12-015. Use of the oral dispenser was validated in a label comprehension study. Refer to Section 3.2.R.4 for detailed technical and regulatory information for the graduated oral dispenser and press-in bottle adapter including materials of construction, drawings and controls.



Oral Dispenser: A clear graduated oral dispenser is provided along with the bottle and press-in bottle adapter for use by the patient in dispensing the product. The oral dispenser will allow the patient to draw the desired dose with accuracy. The dispenser consists of two parts, a barrel and a plunger. Graduation scale is printed on the barrel with black printing ink. The single doses of 4.25 mg in 0.85ml and 2.125mg in 0.425ml are printed on the oral dispenser.

- Barrel

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- [redacted]
- Plunger [redacted]

Press-in Bottle Adapter: A clear vented 20 mm press-in bottle adapter is provided along with the oral dispenser for dispensing Dronabinol Oral Solution from the bottle. At the time of first use, a press-in adapter is fitted on to the bottle and kept there for the entire duration of use. The press-in bottle adapter allows the user to draw the liquid medication with the oral dispenser.
The press-in bottle adapter is manufactured from [redacted].

Regulatory fact sheet
[redacted] confirms that [redacted], as manufactured and shipped from [redacted] facilities, can be used in complying with Title 21 of the Code of Federal Regulations, CFR, per the conditions below:
[redacted] confirms that [redacted] is produced with raw materials and operating practices that would not render the [redacted] unsafe or unsuitable for contact with food within the meaning of Sections 402 and 409 of the Federal Food, Drug, and Cosmetic Act and its implementing regulations including the Good Manufacturing Practice regulation, 21 CFR §174.5 "General Provisions applicable to indirect food additives".

3. <u>Documents Reviewed:</u>
- ICC1500288 consult request from CDER
- NDA 205525 application.
- LOA to review DMF [redacted]
- DMF [redacted] for the oral dispenser and press-in adapter by [redacted].
- The Applicant's response to CDRH's additional information request dated August 10, 2015.
- The Applicant's response to CDRH's biocompatibility additional information request November 2015 and January 2016.

4. <u>CDRH Review and Comments:</u>
This review was limited to the proposed oral dispenser and press-in adapter combination product presentation in NDA 205525.

Reference ID: 3907554

DMF [redacted] for the oral dispenser and press-in adapter by [redacted] DMF [redacted] contains complete device materials information.

- **Performance Tests in NDA 205525 for the oral dispenser and press-in adapter.**

Test name: Dose Accuracy: Accuracy of Dronabinol Oral Solution Dispensing with the oral dispenser proposed for commercialization

Results:

- The visual inspection of [redacted] syringes showed no physical defects on the syringes used in the study. Accuracy of dispensing data indicates that the error was no more than 1.464% away from target volume of 0.85 mL, individual dose dispensed by [redacted] Syringe was not greater than 2.5 % of "Target volume".
- Accuracy of Syringe conforms to 2011 U.S.P 34/NF 29, Teaspoon, Chapter <1221> specification, and 2014 U.S.P 37/NF 32, "Deliverable Volume", Chapter <698>. "Deliverable Volume". Within the range of [redacted]%.

Conclusion:

[redacted] oral dispenser is suitable for Dronabinol Oral Solution and allows accurate dispensing of the product.

Test Name: Accessibility of Dosing and Compatibility between Oral Dispenser and Press-In Bottle Adaptor.

Results:

Visual inspection Oral Dispenser suggests that there were no physical defects on the oral dispensers used the study.

Accessibility of dosing/Dispensing test demonstrated that 65 to 67 accurate doses of 0.425mL and 33 to 34 accurate doses of 0.85 mL can be delivered using [redacted] Oral Dispenser and press in bottle adapter.

No compatibility issues were observed during the entire study while withdrawing doses using press in adapter and [redacted] Oral Dispenser.

Conclusion:

Dispensing data indicates that a minimum of 65 doses of 0.425mL 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.

- **Cleaning Instructions for the oral dispenser:** In the instructions for use: Remove the plunger from the syringe barrel. Rinse the syringe barrel and plunger with warm [redacted] water after each use and let air dry. When the syringe barrel and plunger are dry, put the plunger back into the syringe barrel for the next use.

[redacted]

Previous deficiencies and information request with Applicant's Responses:

- **Information request from the CDRH/ODE/GHDB lead consult review of the oral dispenser and press-in adapter on August 10, 2015:**

1. Please provide a sample of the oral dispenser and press-in adapter for our review.

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Applicant's Response: Two samples of the proposed product, including the: packaging, multi-dose container, graduated oral dispenser/syringe, and press-in bottle adapter for dose dispensing accompany this response.

CDRH's Response: The Applicant provided a sample of the device components. All the components are compatible and function as intended and per the instructions for use.

2. In NDA 205525 you have provided limited device information for the oral dispenser and press-in adapter. You have referenced DMF (b) (4) for additional information. The information obtained in DMF (b) (4) for the oral dispenser and press-in adapter is the materials of construction for these devices. I was not able to locate performance bench test reports in the DMF and only one bench test report for dose accuracy in NDA 205525. Please provide complete functionality performance bench test reports for the oral dispenser and press-in adapter in NDA 205525. As well as performance test reports to demonstrate compatibility of the oral dispenser and press-in adapter and how many times the adapter can be accessed by the oral dispenser.

Applicant's Response: To address the FDA's request to conduct bench studies on the functionality performance of the syringe and adapter combination, we performed a bench study. A description of this study and its results are included in the report RD.0002 accompanying this submission. An updated section 3.2.R.4 is also provided.
Please note, for DMF completeness, (b) (4) also provided a Failure Modes and Effects Analysis (FMEA) for the manufacturing process of the device. We enclose this for your information.

CDRH's Response: The Applicant provided 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.

- **Information request from the CDRH/ODE/GHDB Biocompatibility consult review of the oral dispenser and press-in adapter:**

1. You stated you performed a chemical stability study in which the Dronabinol Oral Solution was held in the dispensing syringe for 8 hours and the impurity levels were assessed (table 1 on pg. 3 of 3.2.R.4). The sponsor should provide the data for the leached substances for this test. Alternatively, the sponsor can clarify the use-life of the syringe (ie. how many times the syringe will be reused and/or over what period of time) and perform a risk assessment of the leachables after an incubation period with the drug, consistent with the use-life.

Applicant's Response: *An extractable study was performed using the oral dispensing syringe using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the syringe components for 24 hours (Extractable Report referenced (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose of (b) (4) mL, an analytical evaluation threshold (AET) and reporting threshold were calculated for the amount of extractable per device.*

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Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds based on allowable maximum dose of (b) (4) *mL (Table 1). Toxicological evaluation showed that PDE for all the compounds th*at can possibly be extracted under reflux conditions were below the acceptable daily intake (ADI) level (Toxicity Evaluation Report (b) (4)-SR025A, Table 2 and Summary Memo dated November 12, 2015).

CDRH's Response: The Sponsor's response is adequate.

2. The directions for use state that the opened bottle can be stored for up to 28 days; however, it is unclear if the adapter will be re-used in subsequent bottles of Dronabinol. The sponsor should clarify the use-life of the adapter and provide leachables/extractables testing using Dronabinol as the solvent for the adapter according to the use-life conditions. Alternatively, the sponsor can use accelerated conditions (ie. 50° C for 72 hours) to assess the possible leachants/extractants resulting from the interaction between the drug and the adapter.

Applicant's Response: *It is not recommended to re-use the adapter in subsequent bottles of Dronabinol Oral Solution. For each new prescription a new unit of use container is delivered to the patient. The unit of use container includes a 30mL light-resistant bottle containing 150mg of Dronabinol (4.25 mg / 0.85 mL), an oral syringe, and an adapter. It is clearly indicated on the carton submitted in this sequence that the product should be dispensed in this unit-of use container.*
An extractable study was performed using the press-in bottle adapter using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the bottle adapter for 24 hours (Extractable Report (b) (4) *-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose an analytical evaluation threshold (AET) and reporting threshold was calculated for the amount of extractable per device.*
Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds. Toxicological evaluation showed that PDE for all the compounds that can possibly be extracted under reflux conditions was below the acceptable daily intake (ADI) level. Refer to Toxicity Evaluation Report (b) (4) *-SR025A, Table 1, Table 2 and Summary Memo dated November 12, 2015 for detailed information.*

The targets for leachables were identified based on the extractable characterization study. The leachables analysis was performed on drug product sample that was held in the presence of bottle adapter for 28 days at ambient conditions. The bottle was placed in horizontal orientation to provide constant contact of bottle adapter with drug product solution. None of the potential leachables were detected in this sample (Leachable Report (b) (4) -M0075). Based on the results of leachable study the bottle adapter can APPEARS THIS WAY ON ORIGINAL

CDRH's Response: The Sponsor's response is adequate.

3. The sponsor has provided an USP <661> testing summary for the syringe barrel and plunger as well as the bottle adapter; however, the information in this summary was limited. The sponsor should provide their test protocol(s), including but not limited to the specific solvents used, extraction time, extraction ratio and extraction conditions. They should also provide an evaluation

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of their results including an explanation as to why the amount (mg) of nonvolatiles extracted does not present a safety concern to the patient.

Applicant's Response: *In the previous response dated August 28, 2015, Insys provided experimental details of USP <661> testing. This is a gravimetric test and the limits have been developed by USP in order to assess suitability of material being used in the manufacture of components used.*
For the evaluation of safety of any leachables that may be present due to exposure to syringe and bottle adapter, Insys conducted extractable characterization and leachable identification studies as outlined in response to Questions 9 and 10. A leachables study showed that only one compound (b) (4) *was observed above the analytical evaluation threshold for the syringe sample and the amount present is well below the acceptable daily intake. The bottle adapter did not show any leachables present above AET. Based on this analysis leachables expected to be present due to syringe and bottle adapter contact are well below any toxicity concern.*

CDRH's Response: The Sponsor's response is adequate. This deficiency has been resolved.

4. The sponsor should clarify if the adapter and/or syringe were sterilized.

Applicant's Response: The adapter and syringe are not sterilized as for the oral administration sterilization is not required.

CDRH's Response: The Sponsor's response is adequate.

5. Mid-Cycle Additional Information CDRH/ODE request for the Oral Dispenser and Press-In Adapter:

The Applicant has adequately responded to the previous additional information requests. They have stated that the will be providing the requested biocompatibility test reports around November 9, 2015. During the review of the Applicant's response two additional deficiencies were noted.

Please provide the following to the Applicant regarding the Oral Dispenser and Press-In Adapter:

1. The information describing the nature and duration of patient contact of the Oral Dispenser and Press-In Adapter device components could not be located within the submission. Please provide a description of the category and duration of contact of each device component (ie. adapter and syringe).

   Applicant's Response: *Category of the device is Surface Device. Based on the review of the tapes of the label comprehension study submitted on June 01, 2015, the total amount of time spent contacting the adapter or syringe was approximately five minutes. Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h). Please refer to the report of the label comprehension study, submitted on June 01, 2015, for details on this study.*

Reference ID: 3907554

2. Additionally, the reviewer was unable to locate an evaluation of the biocompatibility of the Oral Dispenser and Press-In Adapter device components. Please provide the appropriate biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. Please provide the test summaries, test method (including sample preparation and acceptance criteria), full test reports, and an analysis of the results.

Applicant's Response: *Please find the accompanying letter from the manufacturer of the adapters and syringes attesting these products are currently being used for OTC, Rx, and Oral Liquid applications. They are Class I Medical Devices and are exempt from 510K Pre-Market Submission requirements. The manufacturer,* (b) (4) *has provided USP Class VI testing for the* (b) (4) *used in the manufacture of barrel for oral dispenser.*
As Dronabinol Oral Solution is now classified as a combination product, Insys will initiated the biocompatibility study with the oral dispenser and bottle adapter and anticipate submission of results to FDA by middle of January 2016.
Updated Insys Response
In response to this question, Insys initiated biocompatibility studies with the oral dispenser and bottle adapter.
Based on the FDA draft guidance, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" issued on April 23, 2013, the oral dispenser and adapter are both classified as surface devices and have limited contact. Biocompatibility testing needed are Cytotoxicity, Sensitization, and Intracutaneous Reactivity. These tests were performed by contract testing lab (b) (4) *under pre-approved protocols and results are summarized below. Devices meet the requirement of biocompatibility as defined in the guidance. Please note, section 3.2.R.4 was updated to describe biocompatibility study results as well.*
1) Cytotoxicity: The test articles, Oral Dispenser and Adapter, were evaluated separately for potential cytotoxic effects using an in vitro mammalian cell culture test. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A single preparation of the test article was extracted in single strength Minimum Essential Medium (lX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly extracted. Triplicate mono layers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% C02 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration. The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test because the
grade was less than a grade 2 (mild reactivity). Details of the methodology followed and test results are in the attached reports 15T_67759_02 (dispenser) and 15T_67937_02 (adaptor).
2) Sensitization: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices -Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article

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was not considered a sensitizer in the guinea pig maximization test. Details of the methodology followed and test results are in the attached reports 15T_67759_05/15T_67759_06 (dispenser) and 15T_67937_05/15T_67937_06 (adaptor). 3) Intracutaneous Reactivity: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively. Details of the methodology followed and test results are in the attached reports 15T_67759_03/15T_67759_04 (dispenser) and 15T_67937_03/15T_67937_04

CDRH Biocompatibility Review Summary: All deficiencies have been resolved through interactive review. The sponsor has provided all requested information and test reports. The information within the submission and supplements was adequate to perform a biological evaluation of the devices. The consulting reviewer does not believe that use of the device will result in a toxicological response.

CDRH Final Recommendation: The Applicant has adequately addressed all CDRH deficiencies.

Addendum:

Post Final Review Outstanding Issues Re: Oral Syringe:

March 3, 2016: DMEPA proposed a revised dosing and syringe.

Email sent by CDER: DMEPA has drafted a proposal regarding revised dosing. This is now in SharePoint under the folder DMEPA proposal. Please take a look at your earliest convenience so that a final IR can be drafted to the Sponsor by tomorrow, March 4, 2016.

March 4, 2016: CDRH's Response regarding (b) (4)

CDRH does not agree (b) (4) Our biocompatibility and device performance review were based on the documents provided in NDA 205525 Dronabinol application and all our deficiencies were resolved by the applicant. Oral dispensing devices under CDRH/ODE are classified as Class I exempt devices under 21 CFR 880.6430 and the applicant is not required to submit documents or a 510(k) submission to be reviewed for safety and effectiveness. (b) (4)

(b) (4)

Reference ID: 3907554



CDRH would be required to review any new documents and biocompatibility/performance test reports (b) (4) for NDA 205525 prior to making a decision. Please let me know if you have any questions.

March 15, 2016: Teleconference with the Sponsor regarding DMEPA's recommendations to the oral syringe graduation markings.
CDER and CDRH participated in a teleconference with the sponsor today about their revised oral dispenser. In response to our concerns regarding the dosing markings, the sponsor proposes to use an "off-the-shelf" syringe which reflects the preferred dosing markings requested by FDA. The sponsor stated in the tcon that the new syringe is identical to the original syringe covered by (b) (4) DMF (b) (4) We requested that the sponsor submit to the NDA a side by side comparison of the syringe information.
It is anticipated to be submitted on Friday.

March 20, 2016: Additional Documents provided from CDER to review regarding the alternate proposed syringe.
The applicant submitted a formal response to the dosing and administration deficiencies outlined in a discipline review letter (3/11/16) and further clarified in a tcon (3/15/16). The response contains:

1. Module 1.11. Direct comparison of dispensers and certification statement
2. Module 1.14 Proposed labeling and IFU (uploaded to sharepoint) March 20 Sponsor Proposed PI IFU
3. Module 3: Quality information on Syringe and Extractable testing

March 21, 2016: CDRH Response provided to CDER.
Based on the documents provided by applicant the current syringe and proposed syringe are identical in design/dimensions, materials/ink, DMF (b) (4) and processing. Therefore, the performance bench testing, biocompatibility and drug compatibility testing that has been performed on the syringe that we reviewed under NDA205525 (41-0236-001) can be leveraged for the evaluation of the proposed to-be marketed syringe (41-0008-163).

Reference ID: 3907554

The only change in the syringe is on the barrel graduation markings per DMEPA's request: "[redacted] (b) (4) 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."

Please contact Kathleen FitzGerald at (301) 796 – 6292, if you have any questions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Kathleen E. Fitzgerald -A Digitally signed by Kathleen E. Fitzgerald -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -A Date: 2016.03.23 13:46:54 -04'00'
Team-Leader Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	

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

/s/

MAUREEN D DEWEY
03/24/2016

HUMAN FACTORS STUDY & LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 24, 2016
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 205525
Product Name and Strength:	Syndros (dronabinol) Oral Solution 4.25 mg/0.85 mL (5 mg/mL)
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Insys Therapeutics, Inc.
Submission Date:	June 1, 2015 & September 28, 2015
OSE RCM #:	2014-1997
DMEPA Primary Reviewer:	Matthew Barlow, BSN, RN
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

Reference ID: 3907472

1 REASON FOR REVIEW

This review is in response to a request by DGIEP for DMEPA to evaluate the Label Comprehension study results and labels and labeling submitted on June 1, 2015 as a part of the applicant's resubmission package under NDA 205525. DGIEP requested that DMEPA review the Label Comprehension study results, labels, and labeling for areas of vulnerability that may lead to medication errors

1.1 Regulatory History

Insys Therapeutics, Inc. submitted this application as NDA 205525 on August 12, 2014. On October 5, 2014, the application received a Refuse to File due to an incomplete or inadequate pediatric study plan to conduct studies to assess the safety and effectiveness of the product for treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric patients who failed to respond adequately to conventional antiemetic treatments (i.e., failure to address the requirements under the Pediatric Research Equity Act). The applicant resubmitted the application, including results of a Label Comprehension Study, on June 1, 2015. In response to an Information Request, the applicant submitted additional information necessary for a complete review of the product on September 28, 2015 including product samples, participant demographics and individual study results, subjective questioning, mitigation strategies and changes developed and implemented in response to the study results, root cause analysis, and a use-related risk analysis of performance. The requested information was submitted on September 28, 2015.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

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3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Product Design

Insys Therapeutics, Inc. resubmitted an NDA which proposes a 5 mg/mL oral solution dosage form of dronabinol. The reference listed drug (RLD) for this product is Marinol (NDA 018651), which is currently approved as 2.5 mg, 5 mg, and 10 mg capsules. Marinol is indicated in 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. We note that the applicant is pursuing the same indications as the RLD. However, to account for the difference in bioavailability of the proposed formulation compared to the RLD (i.e., 2.125 mg of Syndros is equivalent to 2.5 mg of Marinol, 4.25 mg of Syndros is equivalent to 5 mg of Marinol, and 8.5 mg of Syndros is equivalent to 10 mg of Marinol), the applicant proposes a different dosing for the two indications. Additionally, the applicant proposes to package the 5 mg/mL oral solution in a 30 mL bottle, with an oral dispenser/syringe and a bottle adaptor. The proposed oral syringe has labeled increments of 0.425 mL (2.125 mg) and 0.85 mL (4.25 mg), corresponding to dosing increments for the two indications. We note that the applicant has proposed dosing that is based off of the patient's BSA, and presents the dose in both mg and ml in D&A section. Additionally dose in mg and mg/m^2 was expressed to the hundredth and thousandth decimal place, both of which increases the risk of dosing errors in prescribing and dispensing due to its inherent complexity. Furthermore, we note that doses would need to be rounded to the nearest 2.125 mg increment, which would need to correspond to the nearest 0.425 mL increment, as labeled on the oral syringe. Thus patients/caregivers would need to calculate their doses in increments of 0.425 mL or 0.85 mL in order to draw up their correct dose, if their dose was above 0.85 mL. Given the complicated dosing regimen and corresponding oral syringe, there are concerns for dosing errors.

Label Comprehension Study

As part of their resubmission of the applicant NDA 205525, Insys Therapeutics submitted results of their Label Comprehension Study on June 1, 2015. DMEPA evaluated the results of the Label Comprehension study to determine if patients and/or caregivers can use the product safely and effectively. The study included a total of 30 participants, who each completed three trials, for a total of 90 trials.

DMEPA noted flaws with regard to the methodology of the Label Comprehension study. Given the dosages that were proposed for the two indications of anorexia associated with weight loss in adult patients with AIDS and nausea and vomiting associated with cancer chemotherapy, the proposed oral syringe that was tested in the Label Comprehension study had two labeled graduation mark of 0.425 mL (2.125 mg) and 0.85 mL (4.25 mg). The two highest dose levels for the anorexia indication are 1.275 mL (0.85 mL plus an additional 0.425 mL) and 1.7 mL (0.85 mL plus an additional 0.85 mL). For the antiemetic indication, the dosage range was even higher, which may require that patients draw up 0.85 mL more than 2 times in order to achieve their required dose. In the study, the participants were not assessed as to whether they would be able to safely and effectively administered doses above 0.85 mL. Although the Applicant conducted a knowledge assessment where participants were asked what they would do if their prescribed dose was greater than 0.85 mL, they were not evaluated to see if they could

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calculate said doses or if they were able to draw up the correct dose using the proposed oral dispenser with a maximum volume of 1 mL. Additionally, the tested Instructions for Use (IFU) instructed patients that "If the prescribed dose is more than 0.85 mL (4.25 mg), repeat steps 5 through 12", which may mislead patients/caregivers to draw up the same amount that they did initially. Furthermore, the applicant did not provide adequate root cause analysis of the errors or any subjective feedback from the participants.

With regard to the results of the study, errors occurred in the following tasks:

1. Ability to open package
2. Ability to draw the solution correctly (plunger to the bottom of the barrel, tip into adapter, bottle upside down)
3. Ability to draw the correct dosage
4. Placement of the tip of the syringe in mouth on top of the tongue
5. Dispense full dose

Ability to open package:

In the second and third trial, two participants failed to close the bottle after first and second use. In the third trial, two of the participants did not close the bottle after second use. This error does not affect the results of the study in terms of the safe and effective use of the product. Step 13 of the proposed IFU states to "(b) (4) the child-resistant cap back on the bottle (See Figure J)" with an associated image. Therefore, no additional modifications to the product or proposed IFU are needed to mitigate this type of error.

Ability to draw the solution correctly:

Although there were errors made by 4 participants in drawing up the dose in the first two trials (see Appendix C for details), by the third trial, all 30 participants drew the solution correctly. Failure to turn the bottle upside down or insert the plunger all the way down may result in delay of treatment as the user would not draw up any drug product, but these errors do not affect the results of the study in terms of the safe and effective use of the product. Additionally, the proposed IFU instructs users to (b) (4) and "Step 7: Turn the bottle upside down (b) (4) firmly inserted into the adaptor", and provides associated images (Figure D, Figure E, Figure F(a)). Therefore, no additional modifications to the product or proposed IFU are needed to mitigate this type of error.

Ability to draw the correct dosage:

Although there were errors by 10 participants in drawing up the correct dose in the first two trials (see Appendix C for details), all participants were able to draw up the correct dosage in the third trial. We noted from the study results that four participants drew up 0.85 mL instead of the ordered 0.425 mL. Although a root cause analysis was not performed, the labeling of the oral syringe with both milligram and milliliter 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, we note that the applicant did not test participants' ability to calculate and draw doses higher than 0.85 mL. As patients/caregivers would need to calculate their doses in increments of 0.425 mL or 0.85 mL due to the proposed dosing of the product and

corresponding design of the syringe, we were concerned about the risk of dosing errors since this user task was not tested. Due to these errors observed in the study as well as concerns for dosing errors with regard to doses above 0.85 mL, we provided recommendations for the applicant to address these aspects on the oral syringe and the Dosage and Administration section.

Placement of the tip of the syringe in mouth on top of the tongue:

One participant placed the syringe toward the side of his mouth in all three trials. No root cause analysis was provided. However, per the review team, administering the drug on the side of the mouth may increase the risk of no first pass effect, in which the drug can quickly passively diffuse into the blood and enter systemic circulation. The proposed IFU states "Step 12…Place the (b) (4) in the back of your mouth on top of your tongue", with an associated image showing a side-angled view of administering the product (Figure I). Although the instructions are clear, the image can be improved to show the user placing the syringe in the correct location. We provide recommendations in Section 4.2 to address this error.

Dispense full dose:

In the second trial, one participant "pretended" to dispense the liquid correctly as this was the participant who failed to turn the bottle upside down and draw up the product in the syringe. This error occurred due to an error in a previous task, and therefore cannot be assessed.

Label and Labeling

The sponsor submitted the proposed labels and labeling on June 1, 2015 and September 28, 2015. DMEPA noted several safety concerns with Section 2 Dosage and Administration of the Prescribing Information. In Section 2, the dosages were presented in both milligrams (mg) and milliliters (mL). Additionally, dose in mg and mg/m^2 was expressed to the hundredth and thousandth decimal place, both of which increases the risk of dosing errors in prescribing and dispensing due to its inherent complexity. We were concerned that the complexity of the dosing in addition to the design of the syringe would lead to dosing errors. Specifically, we noted that doses would need to be rounded to the nearest 2.125 mg increment, which would need to correspond to the nearest 0.425 mL increment, as labeled on the oral syringe. Furthermore, as discussed briefly above, patients/caregivers would need to calculate their doses in increments of 0.425 mL or 0.85 mL in order to draw up their correct dose, if their dose was above 0.85 mL. This task was not tested in the applicant's label comprehension study.

We discussed these concerns with the clinical team as well as revisions to Section 2 and the oral syringe to help alleviate some of these concerns. In a Discipline Review letter sent to the Sponsor, dated March 11, 2016, the review team outlined these concerns regarding the risk of dosing errors due to the complexity of the dosing regimen and the design of the oral syringe (see Appendix F). We recommended revisions to the PI to provide a single metric unit of measure (mg and mg/m^2) and rounding of all doses to the tenth decimal place (i.e., nearest 0.1 mg increment). Additionally, we recommended providing a formula for the nausea and vomiting indication to aid health care providers in calculating and rounding the starting dose to the nearest 0.1 mg increment. Furthermore, we recommended that the applicant re-label the

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oral syringe with 0.1 mL increments, to align with the revised Dosage and Administration section of the PI. Such revisions to the syringe would be consistent with standard 1 mL syringes currently available on the market. The specific recommendations to mitigate these concerns were provided in the Discipline Review Letter and can also be found in Section 4.2. In a teleconference with the applicant, held on March 15, 2016, the applicant agreed to the above recommendations and submitted revised labels and labeling on March 20, 2016.

DMEPA notes that the oral syringe that will be co-packaged with the product is a standard 1-mL oral syringe, and there are other currently marketed oral solutions that use a similar dosing device, with which patients are able to measure and administer their doses. Given the implementation of the above recommendations with regard to the revised dosing syringe and Dosage and Administration section, we don't think another label comprehension study is needed by the applicant. However, we note that the revised container labels, carton labeling, and Instructions For Use, submitted on March 20, 2016, can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

4 CONCLUSION & RECOMMENDATIONS

Although errors occurred in the Label Comprehension study, revisions were made to the syringe to align with a standard 1 mL oral syringe, along with concurrent revisions to the Dosage and Administration section of the Prescribing Information. 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. However, the proposed syringe label, carton labeling, Instructions for Use can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Provide guidance on rounding doses to the nearest milliliter in Section 2.3. For example:

   Calculate the starting dose by following the steps below:
   - Starting dose (mg) = Patient BSA (m^2) x 4.2 mg/m^2
   - Round dose to the nearest 0.1 mg increment
   - If converting doses to milliliters (mL), round dose to the nearest 0.1 mL increment. Provide both units of measurement (mL) and (mg) on the prescription.

4.2 RECOMMENDATIONS FOR INSYS THERAPEUTICS, INC.

Following the deficiency letter, we received revised labels and labeling on March 20, 2016. We recommend the following be implemented prior to approval of this NDA:

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A. Instructions for Use

1. Revise Figure I to clearly show the user placing the syringe in the correct location. As currently presented, the image is from a side-angle and may not be demonstrating the correct positioning in a clear manner.
2. We recommend adding instructions for the user to take a drink of water immediately following oral administration of the product, to mitigate the potential for sublingual drug absorption. This is consistent with the bioequivalence study method.
2. We recommend using only milliliters as the unit of measurement in the Instructions for Use as it is designed for patients and corresponds to the units on the syringe. Additionally, the revised oral syringe measures doses in increments of 0.1 mL per the Prescribing Information to a maximum of 1 mL. Therefore, in Step 7, we recommend revising to (see track changes version below):

   "(b) (4)
   .

   For example, if your dose is 1.2 mL, you will need to draw a 1 mL dose followed by a 0.2 mL dose."

   (b) (4)

3. We recommend using only milliliters as the unit of measurement in the Instructions for Use as it is designed for patients and corresponds to the units on the syringe. Therefore, in Step 12, we recommend revising to (see track changes version below):

   "If the prescribed dose is more than 1 mL, repeat steps 5 through 12 to draw up the remaining dose until the total dose prescribed is administered. For example, if 1.6 mL is prescribed, take a 1 mL dose first and then an additional dose of 0.6 mL."



B. Carton and Container

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

C. Carton Labeling Only

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Syndros that Insys Therapeutics, Inc. submitted on June 1, 2015 and September 28, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Syndros and the Listed Drug		
Product Name	**Syndros (dronabinol) oral solution**	**Marinol (dronabinol) capsules**
Initial Approval Date	N/A	May 31, 1985
Active Ingredient	Dronabinol	Dronabinol
Indication	Indicated in adults for the treatment of: 1. Anorexia associated with weight loss in patients with AIDS; and 2. Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.	Indicated in adults for the treatment of: 1. Anorexia associated with weight loss in patients with AIDS; and 2. Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
Route of Administration	Oral	Oral
Dosage Form	Oral Solution	Capsules
Strength	4.25 mg/0.85 mL (5 mg/mL)	2.5 mg; 5 mg; 10 mg
Dose and Frequency	• **Anorexia**: recommended adult starting dosage of TRADENAME is (b) (4) (2.125 mg) orally twice daily, one hour before lunch and one hour before supper. If tolerated and further therapeutic effect is desired, the dosage may be increased gradually to (b) (4) (2.125 mg) one hour before lunch and (b) (4) (4.25 mg) one hour before supper. The dose may be further increased to (b) (4) (4.25 mg) one hour before lunch and (b) (4) (4.25 mg) one hour before supper, as tolerated to achieve a therapeutic effect.	• **Anorexia:** Initially, 2.5 mg MARINOL Capsules should be administered orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this 5 mg/day dosage of MARINOL Capsules, the dosage can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. The dosage may be gradually increased to a maximum of 20 mg/day MARINOL Capsules, administered in divided oral doses. • **Nausea and Vomiting Associated**

	• **Nausea and Vomiting Associated with Cancer Chemotherapy**: recommended starting dosage of TRADENAME is [redacted] (4.25 mg/m^2) orally administered 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial effect, as tolerated to achieve a clinical effect, in increments of [redacted] (2.125 mg/m^2). The maximum is [redacted] (12.75 mg/m^2) per dose.	**with Cancer Chemotherapy:** best administered at an initial dose of 5 mg/m^2, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose.
How Supplied	Supplied in a clear, amber-colored glass bottle filled with 30 mL of solution containing 150 mg dronabinol (4.25 mg/0.85 mL), oral syringe, and a push-in bottle adapter.	MARINOL Capsules (dronabinol solution in sesame oil in soft gelatin capsules): • 2.5 mg white capsules (Identified UM)-NDC 0051-0021-21 (Bottle of 60 capsules). • mg dark brown capsules (Identified UM)-NDC 0051-0022-21 (Bottle of 60 capsules). • 10 mg orange capsules (Identified UM)-NDC 0051-0023-21 (Bottle of 60 capsules).
Storage	Store in a refrigerator between 2° and 8°C (36° and 46°F). Once opened, the bottle can be stored at room temperature for up to 28 days.	Should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing.

Table 3 presents revised Dose and Frequency for Syndros that Insys Therapeutics, Inc. submitted on March 20, 2016.

Dose and Frequency	• **Anorexia**:
	  • The recommended adult starting dosage of SYNDROS is 2.1 mg orally twice daily, one hour before lunch and one hour before supper.
	  • If tolerated and further therapeutic effect is desired, the dosage may be increased gradually to 2.1 mg one hour before lunch and 4.2 mg one hour before supper.
	  • Most patients respond to 2.1 mg twice daily, but the dose may be further increased to 4.2 mg one hour before lunch and 4.2 mg one hour before supper, as tolerated to achieve a therapeutic effect.
	  • Maximum Dosage (b) (4) mg twice daily.
	• **Nausea and Vomiting Associated with Cancer Chemotherapy**:
	  • The recommended starting dosage of SYNDROS is 4.2 mg/m2 orally administered 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day.
	  Calculate the starting dose by following the steps below:
	  Starting dose (mg) = Patient BSA (m2) x 4.2 mg/m2
	  Round dose to the nearest 0.1 mg increment
	  • The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial effect, as tolerated to achieve a clinical effect, in increments of 2.1 mg/m2.
	  • Maximum Dosage: 12.6 mg/m2 per dose for 4 to 6 doses per day.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 4, 2015, we searched the L:Drive using the terms, “dronabinol” and “syndros” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous unrelated reviews, as they are all proprietary name reviews.

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APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

1. **Participants:**
    - **a.** 30 adults aged 18 and over
        - **i.** 25 randomly selected general population and five (17%) low literacy level population (having 4th to 8th grade reading skills).
        - **ii.** 16 females and 14 males between 20 and 70:
            1. Under 30 (6 subjects)
            2. 30-39 (5 subjects)
            3. 40-49 (7 subjects)
            4. 50-59 (6 subjects)
            5. 60-69 (6 subjects)
        - **iii.** None had special training in, or a job related to, healthcare.
        - **iv.** All subjects care for themselves and do not rely on anyone else for their personal, physical, or medical needs.
        - **v.** No subjects had disabilities that hindered normal interpretation (i.e. sight impairment, significant mobility limitations, etc.).
2. **Process/Method**
    - **a.** A qualified moderator from (b) (4) conducted the evaluation at either the offices of (b) (4) or a low literacy organization.
    - **b.** Consisted of 1 subject and 1 moderator and was video recorded.
    - **c.** Subjects were told to bring reading glasses if needed, that the test product was placebo, and they were instructed to sign a consent form.
    - **d.** To start the evaluation, the subject was given a bottle of placebo oral solution, an adaptor wrapped in plastic bag, a dosing syringe, and the/an IFU. The test moderator said:
        - **i.** This is a placebo…assume you have been prescribed this product by your health care practitioner.

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ii. Please read the instructions and use the products as if it contained the active ingredients.

e. The subject was told the dose amount to administer. The dose amount was written on paper and spoken orally. The dose amounts were either 0.425 mL or 0.85 mL.

f. The subject was then asked to proceed as they would if they were in their own home.

g. All observations were recorded by the moderator.

h. The subject was asked to repeat the act of dosing with 2 additional dose amounts for a total of 3 dosing measurements.

i. After the subject finished using the placebo, he or she was asked several questions to learn if the information in the instructions was interpreted correctly.

3. Evaluation Factors and Success Criteria→see page 3 of the study.

4. Summary of Findings/Evaluation Results

a. Evaluation Factor One: Ability to open the package.

i. Trial 1: All 30 subjects opened the bottle without harming the unit or themselves.

ii. Trial 2: 28 out of 30 subjects opened the bottle→ 2 subjects didn't close the bottle after the first use.

iii. Trial 3: 26 out of 30 subjects opened the bottle→2 subjects didn't close bottle after the first and second use; 2 subjects didn't close bottle after 2nd use.

b. Evaluation Factor Two: Ability to draw the solution correctly (plunger to the bottom of the barrel, tip into adapter, bottle upside down).

i. 86 out of 90 trials performed correctly.

ii. Trial 1: 29 out of 30 drew solution correctly:

1. 1 subject who failed to draw solution correctly turned bottle on its side instead of upside down

iii. Trial 2: 27 out of 30 subjects drew solution correctly.

1. 1 subject inserted oral syringe back in bottle after 1st dose.

2. 1 subject didn't insert the plunger of syringe all the way down.

3. 1 subject didn't turn the bottle upside down.

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iv. Trial 3: all 30 subjects drew solution correctly.

c. Evaluation Factor Three: Ability to draw correct dosage.

i. 80 out of 90 trials were done correctly.

ii. Trial 1: 24 out of 30 subjects drew correct dosage.

1. 4 subjects drew 0.85 mL instead of 0.425 mL

2. 1 subject drew slightly more than required 0.85 mL due to air bubble.

3. 1 subject drew slightly less than required 0.85 mL.

iii. Trial 2: 26 out of 30 drew the correct dosage.

1. 1 subject drew slightly more than required 0.425 mL due to air bubble.

2. 1 subject was confused between 0.425 mL and the 4.25 mg.

3. The subject who did not turn the bottle upside down did not pull any liquid

iv. Trial 3: All 30 subjects drew correct dosage.

d. Evaluation Factor Four: Placement of tip of syringe in mouth on top of tongue.

i. 87 out of 90 trials done correctly.

ii. 1 subject placed the syringe under his tongue toward side of mouth in all 3 trials.

e. Evaluation Factor Five: Dispensing the full dose of oral solution.

i. 89 out of 90 trials done correctly.

1. In 2nd trial, same subject who has been noted previously, had no liquid in barrel b/c he didn't turn bottle upside down, however he pretended to dose liquid correctly.

f. Evaluation Factor Six: Comprehension of Dosing directions and warnings.

i. No pass/fail criteria were assigned to these factors→After the 3rd trial was done, the test administrator asked each subject the following questions:

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a. What would you do if your prescribed dose was more than 0.85 mL (4.25 mg)?
   - Twelve of the thirty subjects (12 out of 30) repeated the instructions as written on the instruction sheet (repeat steps 3 through 8).
   - Other common responses given were:
     - Ask doctor (4) or pharmacist (2)
     - Do the math or add the numbers together to get the total dose (8)

b. How soon do you need to take the medication solution once you have drawn it into the dosing syringe from the bottle?
   - Twenty-eight of the thirty subjects (28 out of 30) repeated the instructions as written on the instruction sheet (immediately)
   - The other two subject gave one of the following responses:
     - Whatever is prescribed on the bottle
     - Twice per day

c. Should you remove the adaptor (that you placed in the bottle) after you use the medication?
   - Twenty-eight of the thirty subjects (28 out of 30) said no (per the instruction sheet is to leave the adapter plug in the bottle).
     - Two incorrectly said yes.

d. What do you do with the solution bottle and the dosing syringe when they are not being used?
   - Fourteen of the thirty subjects (14 out of 30) answered as listed in the instruction (keep the oral solution bottle and dosing syringe in the carton).
   - Other responses included one or more of the following:
     - Clean/rinse out the syringe (14 subjects)
     - Put in a spot where kids could not reach or place in medicine cabinet (11 subjects)
     - Store at room temperature (6 subject)
     - Replace cap on bottle (3 subjects)

C.2 Results

1. Summary of Findings/Evaluation Results

a. Evaluation Factor One: Ability to open the package.

i. Trial 1: All 30 subjects opened the bottle without harming the unit or themselves.

ii. Trial 2: 28 out of 30 subjects opened the bottle→ 2 subjects didn't close the bottle after the first use.

iii. Trial 3: 26 out of 30 subjects opened the bottle→2 subjects didn't close bottle after the first and second use; 2 subjects didn't close bottle after 2nd use.

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b. Evaluation Factor Two: Ability to draw the solution correctly (plunger to the bottom of the barrel, tip into adapter, bottle upside down).

i. 86 out of 90 trials performed correctly.

ii. Trial 1: 29 out of 30 drew solution correctly:

1. 1 subject who failed to draw solution correctly turned bottle on its side instead of upside down

iii. Trial 2: 27 out of 30 subjects drew solution correctly.

1. 1 subject inserted oral syringe back in bottle after 1st dose.

2. 1 subject didn't insert the plunger of syringe all the way down.

3. 1 subject didn't turn the bottle upside down.

iv. Trial 3: all 30 subjects drew solution correctly.

c. Evaluation Factor Three: Ability to draw correct dosage.

i. 80 out of 90 trials were done correctly.

ii. Trial 1: 24 out of 30 subjects drew correct dosage.

1. 4 subjects drew 0.85 mL instead of 0.425 mL

2. 1 subject drew slightly more than required 0.85 mL due to air bubble.

3. 1 subject drew slightly less than required 0.85 mL.

iii. Trial 2: 26 out of 30 drew the correct dosage.

1. 1 subject drew slightly more than required 0.425 mL due to air bubble.

2. 1 subject was confused between 0.425 mL and the 4.25 mg.

3. The subject who did not turn the bottle upside down did not pull any liquid

iv. Trial 3: All 30 subjects drew correct dosage.

d. Evaluation Factor Four: Placement of tip of syringe in mouth on top of tongue.

i. 87 out of 90 trials done correctly.

ii. 1 subject placed the syringe under his tongue toward side of mouth in all 3 trials.

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e. Evaluation Factor Five: Dispensing the full dose of oral solution.

i. 89 out of 90 trials done correctly.

1. In 2nd trial, same subject who has been noted previously, had no liquid in barrel b/c he didn't turn bottle upside down, however he pretended to dose liquid correctly.

f. Evaluation Factor Six: Comprehension of Dosing directions and warnings.

i. No pass/fail criteria were assigned to these factors→After the 3rd trial was done, the test administrator asked each subject the following questions:

a. What would you do if your prescribed dose was more than 0.85 mL (4.25 mg)?
- Twelve of the thirty subjects (12 out of 30) repeated the instructions as written on the instruction sheet (repeat steps 3 through 8).
- Other common responses given were:
  - Ask doctor (4) or pharmacist (2)
  - Do the math or add the numbers together to get the total dose (8)

b. How soon do you need to take the medication solution once you have drawn it into the dosing syringe from the bottle?
- Twenty-eight of the thirty subjects (28 out of 30) repeated the instructions as written on the instruction sheet (immediately)
- The other two subject gave one of the following responses:
  - Whatever is prescribed on the bottle
  - Twice per day

c. Should you remove the adaptor (that you placed in the bottle) after you use the medication?
- Twenty-eight of the thirty subjects (28 out of 30) said no (per the instruction sheet is to leave the adapter plug in the bottle).
  - Two incorrectly said yes.

d. What do you do with the solution bottle and the dosing syringe when they are not being used?
- Fourteen of the thirty subjects (14 out of 30) answered as listed in the instruction (keep the oral solution bottle and dosing syringe in the carton).
- Other responses included one or more of the following:
  - Clean/rinse out the syringe (14 subjects)
  - Put in a spot where kids could not reach or place in medicine cabinet (11 subjects)
  - Store at room temperature (6 subject)
  - Replace cap on bottle (3 subjects)

2. **Revisions/Mitigation strategies implemented based on the results**

a. The applicant revised the IFU to include additional pictures reinforcing:

Reference ID: 3907472

i. That the adapter should not be removed

1. Insys has bolded language concerning leaving the adapter (b) (4) in the bottle in addition to the drawing to not remove it.

ii. (b) (4)

1. (b) (4) Also, an example has been added to help calculate the dose when it is greater than (b) (4) mL.

b. Insys has added language regarding how to prevent air bubbles from being drawn up.

c. Insys is also modifying the adapter to make it easier to insert plus the syringe is now wrapped in a plastic (b) (4)

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 4, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Joint Commission Sentinel Event Alert; QAA Community; QAA Acute Care; PA Patient Safety Advisory; ISMP Canada Safety Bulletin; ISMP Nursing Newsletter; ISMP Community Newsletter; ISMP Acute Care Newsletter
Search Strategy and Terms	Match Exact Word or Phrase: Dronabinol

D.2 Results

There were no results found using the search criteria outlined above.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. March 11, 2016 Discipline Review Letter



NDA 205525 DMEPA Discipline Review.pdf

Recommendations previously communicated and discussed with Insys Therapeutics on March 15, 2016:

A. Oral Syringe

1. 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.

B. Section 2 Dosage and Administration

1. In Section 2.2 Anorexia Associated with Weight Loss in Adult Patients with AIDS:
   a. [redacted] (b) (4) present a single metric unit of measure (mg), to minimize the risk of dosing errors [redacted] (b) (4)
   b. Round all mg doses to the tenth decimal place (i.e., nearest 0.1 mg increment). For example, revise:
      "The recommended adult starting dosage of SYNDROS is [redacted] (b) (4) orally twice daily…" to read
      "The recommended adult starting dosage of SYNDROS is 2.1 mg orally twice daily…"
2. In Section 2.3 Nausea and Vomiting Associated with Cancer Chemotherapy in Adult Patients Who Failed Conventional Antiemetics:
   a. [redacted] (b) (4) present a single metric unit of measure (mg/m^2).
   b. Round all mg/m^2 doses to the tenth decimal place (i.e., nearest 0.1 mg increment).
   c. Provide a formula to aid the practitioner in calculating a starting dose along with instructions for the practitioner to round the starting dose to the nearest 0.1 mg increment (if the oral dispenser will be relabeled with 0.1 mL increments for the smaller black lines) [redacted] (b) (4)

d. Similarly, provide instructions for titration of doses and rounding.
For example:

The recommended starting dosage of SYNDROS is 4.2 mg/m^2 orally administered 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day.
Calculate the starting dose by following the steps below:

- Starting dose (mg)= Patient BSA (m^2) x 4.2 mg/m^2
- Round dose to the nearest 0.1 mg increment

C. Instructions for Use (IFU)

1. Revise the proposed Instructions for Use to adequately instruct patients on how to draw up dosages using the 1 mL oral dispenser that exceed (b) (4) mL.
2. Round doses, as appropriate and consistent with Section 2 of the PI, given the comments above about the oral dispenser markings.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post-market medication error data, we reviewed the following Syndros labels and labeling submitted by Insys Therapeutics, Inc. on March 20, 2016.

- Container Label
- Carton Labeling
- Instructions for Use
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)



[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.


(b) (4)

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/s/

MATTHEW J BARLOW
03/24/2016

MISHALE P MISTRY
03/24/2016

LUBNA A MERCHANT
03/24/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality
Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch

DATE:	October 26, 2015 Update: February 18, 2016 **Updated: March 21, 2016**
TO:	Maureen Dewey, CDER/OND/ODEIII/DGIEP, WO22 RM5232 Maureen.Dewey@fda.hhs.gov Julie G. Beitz, CDER/OND/ODEIII/DGIEP, WO22 RM5214 Julie.Beitz@fda.hhs.gov Office of combination products at combination@fda.gov
Through:	For Francisco Vicenty, Branch Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3425
From:	Bleta Vuniqi, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429
Applicant:	Insys Therapeutics, Inc. 1333 South Spectrum Boulevard, Suite 100 Chandler, AZ, 85286 FEI# 3010878756
Application #	NDA 205525
Product Name:	Dronabinol Oral Solution
Consult Instructions:	Evaluate the Dronabinol Oral Solution documents provided by the applicant on quality system requirement 21 CFR 820, and determine if an inspection of the manufacturing facilities

Viky Verna -S
Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.03.21 16:46:53 -04'00'

is required.

Update: evaluate the firm's response to the deficiencies sent on October 26, 2015

Update: Evaluate the firm's response to the deficiencies sent on February 18, 2016

Background:

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205525 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:

Dronabinol Oral Solution is supplied as a single size multi-dose container comprised of a 30 mL glass bottle with a 20-mm child-resistance cap. For tamper evidence, the bottle is wrapped with a PVC body band, and packaged in a suitable size carton along with a graduated oral dispenser for dose dispensing.

The proposed indication is for the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.





Table 1: 30 mL Bottle Control Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Overflow volume	Complies	Volumetric
Closure fit	Fits with the 20 mm child-resistant cap	Visual
Material verification	Clear Amber (b) (4) Glass	Visual verification and supplier CoA verification

Table 2: Child Resistant Cap Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Outer cap and inner shell material/color verification	Complies	Visual verification and CoA verification
Closure fit	Fits with the 30mL glass bottle	Visual
Identification of Teflon layer[a]	IR spectrum obtained for the sample has similar maxima and minima of IR absorption as the reference spectrum[b]	IR Spectroscopy

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

2. Based on the information provided, it could not be determined which facility was responsible for developing the design specifications of the device constituent part, and which facility is maintaining the design history file.

3. The description of the manufacturing activities of the finished combination product was not provided. The application did not include information on how and where the finished combination product would be assembled. No information was provided on acceptance activities.

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. With regards to information being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted. Also, more information will be needed from the applicant prior to making a decision about which facility or facilities would potentially need to be inspected.

Regulatory history evaluation

After reviewing the application, the (b) (4) site located at (b) (4) was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that a device inspection conducted on (b) (4), revealed multiple deficiencies and was classified VAI. The inspection focused on the OEM liquid dispenser [syringe] product. The following QSIT subsystems were covered during the inspection: Management Controls, CAPA, Design Controls, P&PC, Document Controls and Purchasing Controls. A 5-item form FDA 483 was issued to the firm at the conclusion of the inspection. The observations included CAPA, complaints, calibration, and document control.

Determination whether an inspection of the manufacturing facilities is required will not be made at this time until the firm provides the additional information related to the finished combination product manufacturing activities.

Update:

The firm confirmed (b) (4) located at (b) (4), is the primary supplier and manufacturer of oral dispenser and press in bottle adapter. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. FACTS revealed that the firm is listed a "not a workload obligation". The firm is registered with FDA as a "Manufacturer". The firm is not responsible for manufacturing the final combination product; therefore, an inspection is not required for this firm.

Additionally, the firm noted that the drug product manufacturer and the final combination product manufacturer is DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. The most recent inspection was performed on (b) (4) This inspection was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) No FDA-483, Inspectional Observations, was issued and the inspection was classified as NAI. The previous inspection of the firm was conducted on (b) (4) This was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) This inspection covered the new facility, equipment, and process and associated controls including automation, analytical, environmental, microbiology, and formulation and testing of (b) (4) An FDA-483 was issued, and the inspection was classified VAI. The district recommended approval of ANDA (b) (4) ANDA (b) (4) An inspection was also conducted on (b) (4) and covered GMPs of sterile and non-sterile dosage forms, as well as Pre-Approval coverage for NDA (b) (4) (b) (4) filed to transfer manufacture and testing of the finished product to this site. This inspection is classified NAI and approval was recommended for NDA (b) (4) The firm is responsible for manufacturing the final combination product; therefore, an inspection is required for this firm. CDRH/OC recommends a post-market approval inspection of DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application NDA 205525 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product and it is requested that the below be communicated to the firm:

1. Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

   A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide all device information

pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (Management Controls, Design Controls, Purchasing Controls and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

Firm's response:

The applicant noted that the combination product is manufactured at DPT Laboratories, Ltd. Therefore, the firm provided DPT procedures.

Management Control (21 CFR 820.20):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control (21 CFR 820.30):

(b) (4)

(b) (4)



The information provided by the firm has adequately addressed the requirements of 21CFR 820.30.

Purchasing Controls (21 CFR 820.50):

(b) (4)



(b) (4)

The information provided by the firm has inadequately addressed the requirements of 21CFR 820.50.

Deficiencies to be conveyed to the applicant:
Insys Therapeutics, Inc. is responsible for the final combination product. Your November 30, 2015 response noted "(b) (4) " Please provide a description of your supplier evaluation process and a description of your purchasing controls.

Update: 03/21/2016 – Firm's Response

The firm provided SOP.QA.0003 "Supplier Qualification". (b) (4) **The information provided by the firm has adequately addressed the requirements of 21CFR 820.50.**

Corrective and Preventive Action (CAPA) (21 CFR 820.100):

The firm noted the CAPA system is managed via Trackwise. DPT-SOP-03126, "DPT Quality Deviation, Investigation and CAPA Procedure" and



The information provided by the firm has adequately addressed the requirements of 21CFR 820.100.

2. In your response, please provide the name of the facility or facilities that perform the manufacture of the combination product and constituent parts including each facility's responsibility. Additionally, your response should include the facility that was responsible for developing the Dronabinol Oral Solution design specifications, and the facility that maintains the design history file for the finished combination product. Lastly, please provide the name of the facility or facilities that maintains the records for Design Controls; Corrective and Preventive Action; and Purchasing Controls.

Firm's response:

The applicant provided a table containing the name of the facilities that perform the manufacture of the commercial combination product and constituent parts, including each facility's responsibility.

Name of the facility	Responsibility
(b) (4)	Primary supplier of oral dispenser and press in bottle adapter
DPT Laboratories, Ltd. 1200 Paco Way Lakewood, NJ 08701	(b) (4) manufacturing, packaging and labeling, analytical release and alternate stability testing site – Syndros Oral Solution
(b) (4)	Primary supplier of clear amber (b) (4) glass 30 mL bottle
	Primary supplier of white polypropylene child - resistant cap lined with (b) (4) liner (b) (4) liner coated with a Teflon film)
	Primary supplier of (b) (4) cap liner (b) (4) liner coated with a Teflon film) (b) (4)

The firm noted DPT maintains records of design controls or specifications, CAPA and Purchasing controls with oversight from Insys Therapeutics. DPT and Insys Therapeutics have a Quality Agreement in place.

3. The information provided was insufficient to verify that the acceptance activities conducted on supplied device constitutes parts to ensure the safety and effectiveness of the finished combination product. Additionally, the descriptions of the manufacturing activities of the finished combination product were not provided. The application did not include information on how the finished combination product would be assembled.

Firm's response:

Acceptance criteria for incoming controls performed by DPT site for the device components were included in NDA Section 3.2.R.4.6.

Table 5: Oral Dispenser Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification
Graduations Accuracy	(b) (4)	Gravimetric

Table 6: Press-in bottle adapter Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification

Device manufacturer ((b) (4) performs the release testing on the device components prior to shipment to DPT. During the development, Insys Therapeutics also performed device functionality testing to confirm the suitability, safety and effectiveness of the finished combination product and results were provided in NDA (refer to Sections 3.2.R.4.3 and 3.2.R.4.4).

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application Dronabinol Oral Solution and has the following recommendations:

Application Dronabinol Oral Solution is approvable from the perspective of the applicable Quality System Requirements.

The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. In order to meet the PDUFA date CDRH/OC recommends a post-market approval inspection of DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701

Bleta Vuniqi -S

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Date: 2016.03.21 16:50:21 -04'00'

Bleta Vuniqi

Prepared: BVuniqi: October 26, 2015
Reviewed: VVerna: October 28, 2015
Revised: BVuniqi: February 29, 2016
Reviewed: VVerna:March 1, 2016
Revised: BVuniqi: March 21, 2016
Reviewed: VVerna March 21, 2016

CTS No.: ICC1500308

Response: CTS No.: ICC1600112

NDA 205525

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/s/

MAUREEN D DEWEY
03/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring MD 20993

MEMORANDUM TO FILE

From: Tracy Peters, PharmD
Associate Director for Labeling, Acting
The Division of Neurology Products (DNP)

Through: Billy Dunn, M.D.
Division Director
The Division of Neurology Products (DNP)

To: The Division of of Gastroenterology and Inborn Errors Products (DGIEP)
Joette Meyer, Pharm.D., Associate Director for Labeling
Maureen Dewey, Regulatory Project Manager

Drug: Syndros (dronabinol) oral solution, 4.25 mg/0.85 mL

NDA: NDA 205525

Indication(s): For the treatment of adults with:

- 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.

Materials Reviewed:

- Prescribing Information for dronabinol oral solution submitted September 28, 2015 (revised from June 1, 2015, submission) – see Appendix 1
- Prescribing Information for Marinol (dronabinol) Capsules –see Appendix 2

BACKGROUND

On August 12, 2014, Insys Therapeutics, Inc. submitted a New Drug Application pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dronabinol Oral Solution. The original application was not sufficiently complete to permit a substantive review, as stated in the letter dated October 10, 2014. The application was resubmitted on June 1, 2015, and filed. The Referenced Listed Drug for the 505(b)(2) application is Marinol (dronabinol) capsules, which was approved May 31, 1985.

On December 8, 2015, DNP received a request for consultative review from DGIEP:

> *Marinol, relates to the CNS effects of the product, including seizures* (b) (4) *and other central nervous system reactions (CNS), including effects on the ability to drive or operate machinery. Given DNPs experience with labeling other products with CNS adverse reactions (ARs), we would appreciate your assistance in revising/drafting wording for the Warnings and Precautions section regarding these ARs. We would like to update the labeling to be updated to be consistent with products that have a similar AR profile, including updating outdated terminology and clarifying the recommendations for risk management.*

REVIEW

The section below states the applicant's language proposed in the September 28, 2015, submission and DNP's recommendations, based on currently approved labeling within our Division, for DGIEP to consider.

A. <u>Applicant Proposed:</u>

(b) (4)

<u>Comments regarding request for risk management recommendations</u>

2. The applicant included (b) (4) The following statement is included in labeling of sumatriptan products and my alert prescribers to the continued possibility of seizures:

"TRADENAME should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold."

Additional comments

3. [redacted] (b) (4) consider moving the placement of the Warning and Precaution from 5.1 toward the end of the Warning and Precaution listing.

4. We recommend revising the language in this subsection to be similar to that listed below:

   "Seizure and seizure-like activity have been reported in patients receiving dronabinol in clinical trials and in the postmarketing experience. [Tradename] should be used with caution in patients with a history of seizure disorder because [Tradename] may lower the seizure threshold. [Tradename] should be discontinued immediately in patients who develop seizures and medical attention should be sought immediately."

   Rationale for the suggested revision:

   a. The Marinol prescribing information states the following:

      "Seizure and seizure-like activity have been reported in patients receiving MARINOL Capsules during marketed use of the drug and in clinical trials."

      [redacted] (b) (4)

   b. The Marinol prescribing information states the following, which is not included in the proposed labeling for dronabinol oral solution:

      "MARINOL Capsules should be used with caution in patients with a history of seizure disorder because MARINOL Capsules may lower the seizure threshold."

      Consider including the description that the drug can lower seizure threshold.

   c. [redacted] (b) (4)

5. [redacted] (b) (4)

6. [redacted]

B. Applicant Proposed:

[redacted] may impair the mental and/or physical abilities required for the performance of hazardous tasks such as driving a motor vehicle or operating machinery. Concomitant use of other drugs that cause dizziness, [redacted], or somnolence such as [redacted] may increase this effect. [redacted] Inform patients not to operate motor vehicles or other dangerous machinery until they are reasonably certain that TRADENAME does not affect them adversely.

Comments regarding request for updating outdated terminology

1. [redacted], consider replacing "[redacted] with "sedation".

Comments regarding request for risk management recommendations

2. The proposed management strategy includes informing patients "not to operate motor vehicles or other dangerous machinery". In addition to driving or operating heavy machinery, there are many other situations where the adverse reactions listed in this subsection can lead to harm. Consider the following statement (example from Fycompa and Aptiom) below for risk management:

   "Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of TRADENAME is known."

Additional comments

3. The following examples are provided for your consideration. In the Prescribing Information for Fycompa and Aptiom, a subsection is titled "Neurological Effects" or "Neurological Adverse Reactions", respectively. Under this subsection, DNP has included the following headings:" Dizziness and Disturbance in Gait and Coordination"; "Somnolence and Fatigue"; and "Risk Amelioration" or "Hazardous Activities", which includes the statement above (#2) for risk management of any activity requiring mental alertness.

4. In support of the recommended examples listed above (#3), a search of PLR Prescribing Information for neurological drugs managed by DNP in which section 5 includes a Warning and Precaution specifically for driving/operating machinery provided three examples. For two examples, Neurontin and Horizant, a dedicated driving study was conducted. The third example,

Exelon, is for the treatment of dementia associate with Alzheimer's disease and Parkinson's disease; the natural progression of the disease itself can cause this impairment.

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

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/s/

TRACY J PETERS
03/20/2016

ERIC P BASTINGS
03/21/2016

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

Drug Utilization Review

Date:	March 15, 2016
Reviewer(s):	Patty Greene, Pharm.D. Division of Epidemiology II (DEPI II)
Team Leader	Mohamed A. Mohamoud, Pharm.D., MPH, BCPS Division of Epidemiology II (DEPI II)
Deputy Director for Drug Utilization:	LCDR Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
Drug Name(s):	Dronabinol
Application Type/Number:	NDA 018651, ANDA 078292, ANDA 079217
Applicant/sponsor:	Multiple
OSE RCM #:	2016-319

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information in this document has been cleared for public release.

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EXECUTIVE SUMMARY

The Division of Gastroenterology and Inborn Errors Products (DGIEP) is reviewing a pending 505(b) (2) application for dronabinol oral solution under NDA 205525/IND 075228. Dronabinol is a synthetic delta-9 tetrahydrocannabinol indicated for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS). It is also indicated for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic treatments.

The sponsor plans to study the effect of dronabinol oral solution on appetite and weight gain in pediatric patients from age 15-17 years with AIDS related anorexia in (b) (4) study. Furthermore, the sponsor also requested a full waiver of pediatric studies among pediatric patients 0-14 years of age due to the small estimated size of this study population. In support of this review, DGIEP requested the Division of Epidemiology II (DEPI II) to provide data on the use of dronabinol with a focus on pediatric patients aged 15-17 years old. Additionally, DGIEP requested data on the top prescribing specialties as well as diagnosis associated with dronabinol use.

In the outpatient retail pharmacy setting, we found that 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.

Our office based physician surveys data shows that dronabinol was 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.

1 INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) is reviewing a pending 505(b) (2) application for dronabinol oral solution under NDA 205525. Dronabinol is indicated for anorexia associated with weight loss in patients with AIDS. It is also indicated for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic treatments.

The sponsor plans to study the effect of dronabinol oral solution on appetite and weight gain in pediatric patients aged 15-17 years with AIDS related anorexia in (b) (4) study. Furthermore, the sponsor also requested a full waiver of pediatric studies among pediatric patients 0-14 years of age due to the small estimated size of this study population. In support of this review, DGIEP requested the Division of Epidemiology II (DEPI II) to provide data on the use of dronabinol among pediatric

patients aged 0-14, 15-17 and adults 18 years and older. Additionally, DGIEP requested data on the top prescribing specialties as well as diagnosis associated with dronabinol use from 2006 to 2015.

1.1 PRODUCT INFORMATION

Dronabinol is a synthetic delta-9 tetrahydrocannabinol indicated 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.[1] Table 1 provides product information for approved dronabinol products included in this review.

Table 1

Product	Application Number	Approval Date	Dosage Form and Strength	Pediatric Use
Marinol® (dronabinol)	NDA 018651	May 31, 1985	*Oral capsule*: 2.5 mg, 5mg, 10mg	MARINOL Capsules are not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. Caution is recommended in prescribing MARINOL Capsules for children because of the psychoactive effects.
Marinol® (dronabinol)	ANDA 078292	June 27, 2008	*Oral capsule*: 2.5 mg, 5mg, 10mg	
	ANDA 079217	June 20, 2014	*Oral capsule*: 2.5 mg, 5mg, 10mg	
	*Marinol is supplied in bottles of 60 capsules			

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. The time periods examined in each data source were dependent upon data availability. Detailed descriptions and limitations of the databases are included in ***Appendix B.***

[1] U.S. Food and Drug Administration: Drugs@FDA. Marinol® Prescribing Information. Accessed February 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs

Reference ID: 3902745

IMS Health, IMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for dronabinol. Sales data for 2015 indicated that approximately 67% of bottles were distributed to outpatient retail pharmacy settings, 29% to non-retail pharmacies, and 4% to mail-order/specialty pharmacies.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Non-retail and mail-order/specialty pharmacies were not included in this analysis.

2.2 DATA SOURCES USED

IMS Health, Vector One®: Total Patient Tracker database was used to provide the nationally estimated number of unique patients who received a dispensed prescription for dronabinol from U.S. outpatient retail pharmacies, stratified by patient age 0-14, 15-17, and 18 and older years from 2006 through 2015, annually.

IMS Health, National Prescription Audit (NPA™) database was used to obtain the nationally estimated number of dispensed prescriptions for dronabinol stratified by top prescribing specialty from U.S. outpatient retail pharmacies from 2011 through 2015, cumulative. The total dispensed prescriptions included new and refill prescriptions of dronabinol.

Encuity Research, LLC, Treatment Answers™, a U.S. office-based physician surveys database was used to obtain diagnoses associated with the use of dronabinol, stratified by patient age (0-14, 15-17, 18+ years), from 2006 through 2015, cumulative. Drug use mentions were for diagnoses were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates.

3 RESULTS

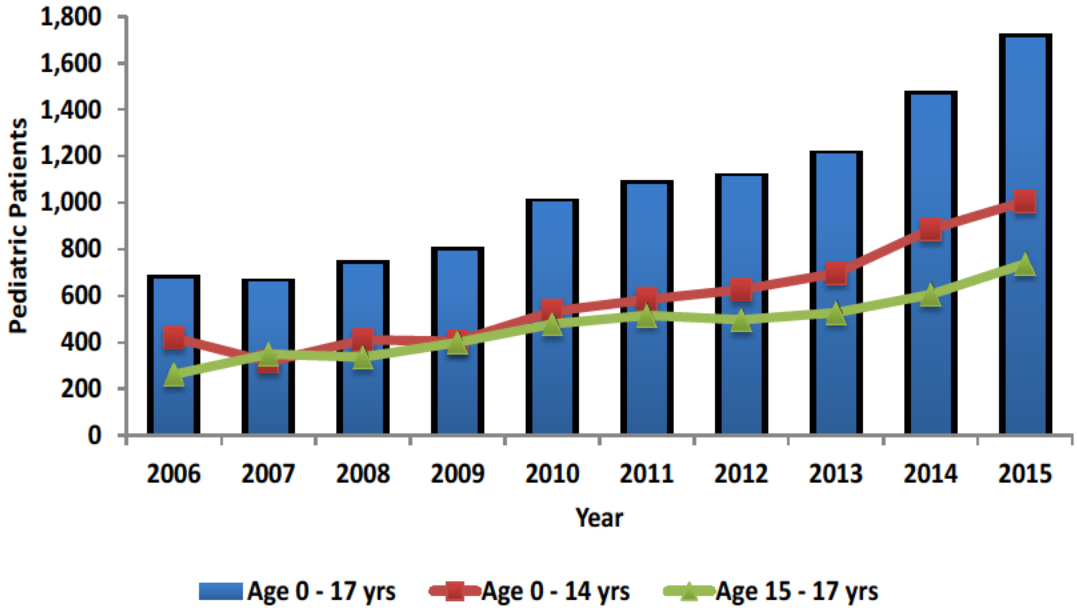
3.1 NATIONAL ESTIMATE OF PATIENTS DISPENSED DRONABINOL IN U.S. OUTPATIENT RETAIL PHARMACIES

Figure 3.1 shows the nationally estimated number of pediatric patients who received a dispensed prescription for dronabinol, from U.S. outpatient retail pharmacies, stratified by patient age (0-14 and 15-17 years), from 2006 through 2015, annually. In 2015, there were 1,700 pediatric patients aged 0-17 years old with a dispensed prescription for dronabinol from outpatient retail pharmacies, a 2.5 fold increase since 2006. The number of pediatric patients aged 0-14 years old increased by more than 2-fold from 420 patients in 2006 to 1,005 patients in 2015. The number of pediatric patients aged 15-17 year old also increased by more than 2-fold from 261 patients in 2006 to 738 patients in 2015.

[2] IMS Health, IMS National Sales Perspectives™. Year 2015. Extracted February 2016. File: NSP 2016-319 Dronabinol channels by year 2-11-16.xlsx

Reference ID: 3902745

Figure 3.1
Nationally estimated number of pediatric patients who received a dispensed prescription for dronabinol, from U.S. outpatient retail pharmacies, stratified by patient age, from 2006 through 2015



Source: IMS, Vector One®: Total Patient Tracker. 2011 - 2015. Extracted March 2016. File:TPT 2016-319 Dronabinol by age 3-4-16.xls

Table 3.1 in Appendix A shows the nationally estimated number of patients who received a dispensed prescription for dronabinol, from U.S. outpatient retail pharmacies, stratified by patient age, from 2006 through 2015, annually. In 2015, there were approximately 98,000 patients with a dispensed prescription for dronabinol from outpatient retail pharmacies, a 30% increase since 2006. Since 2011, the number of adults increased each year from 76,000 patients in 2011 to 96,000 patients in 2015. Adults aged 18 years and older accounted for 98%-99% of total patients receiving a dispensed prescription for dronabinol for the entire review period. Pediatric patients aged 0-17 accounted for 1%-2% annually of total number of patients receiving a dispensed prescription for dronabinol in the outpatient setting from 2006 through 2015.

3.2 PRESCRIBER SPECIALTY

Table 3.2 in Appendix A shows the top prescribing specialties for dronabinol by the number of prescriptions dispensed from U.S. outpatient retail pharmacies, from 2011 through 2015, cumulative. During the time period examined, 1.2 million prescriptions were dispensed for dronabinol from 2011 through 2015. The top prescribing specialties were Internal Medicine at (18% of total prescriptions) followed by Oncology (16% of total prescriptions) and Family Practice (12% of total prescriptions). All other specialties accounted for less than 10% of total prescriptions, respectively. Pediatrics accounted for 0.5% of total dispensed prescriptions (data not shown).

3.3 DIAGNOSES ASSOCIATED WITH USE

Table 3.3 in Appendix A shows the top diagnoses associated with the use of dronabinol by the number of drug use mentions as reported by U.S. office-based physician surveys, stratified by patient age, from 2006 through 2015, cumulative. The most common diagnoses associated with the use of dronabinol among the adult population (ages 18 years and older) were Anorexia (ICD-9 code 783.0) followed by Nausea and Vomiting (ICD-9 code 787.0) during the examined time period. There were no reports of Anorexia (ICD-9 code 783.0) associated with the use of dronabinol among pediatric patients 15-17 years old. No drug use mentions were reported for pediatric patients under the age of 15 years.

4 DISCUSSION

Our findings show that less than 100,000 patients each year received a dispensed prescription for dronabinol from U.S. outpatient retail pharmacies since 2006. The vast majority of use for dronabinol was in adults 18 years and older which accounted for 98%-99% of total patients for the entire review period. Overall, the number of patients with a dispensed prescription for dronabinol was low among pediatric patients aged 0-17 years at less than 1,800 patients annually or 1% to 2% of the total number of patients receiving a dronabinol prescription from outpatient retail pharmacies. We found that the number of pediatric patients aged 15-17 years old with a dispensed prescription for dronabinol increased and ranged from 261 patients in 2006 to 738 patient in 2015. Similarly, patients aged 0-14 years also increased from 420 patients in 2006 to 1,005 patients in 2015. Dronabinol was mainly prescribed by Internal Medicine, Oncology, and Family Practice physicians, respectively.

Our survey results show that dronabinol was commonly mentioned by office-based physicians for the treatment of Anorexia (ICD-9 code 7830) and Nausea and Vomiting (ICD-9 code 7870) in adults 18 years and older. Other diagnoses reported by office based physicians in adults related to cancer treatments or other conditions that may lead to weight loss. Most likely due to the low pediatric utilization of dronabinol in the outpatient setting, there was no office-based physician survey results reported for the use of dronabinol among pediatric patients 15-17 years old associated with anorexia. Additionally, there were no diagnoses reported for pediatric patients 0-14 years old for the review period despite some low patient utilization among this age group.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that dronabinol was distributed primarily to the outpatient retail setting based on the IMS Health, IMS National Sales Perspectives™. The utilization findings in this analysis can only be generalized to outpatient retail pharmacies, and may not apply to other settings of care (i.e. non-federal hospitals or clinics).

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. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and

outpatient data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSION

Despite the relatively low use of dronabinol, pediatric utilization increased by more than 2-fold since 2006. By 2015, approximately 1,700 pediatric patients received a dispensed prescription for dronabinol in the outpatient retail pharmacy setting. Of these patients, approximately 1,000 pediatric patients were aged 0-14 years old and approximately 700 pediatric patients were aged 15-17 years old. Dronabinol was mainly prescribed by Internal Medicine, Oncology, and Family practice physicians to adults 18 years or older for the treatment of medical conditions associated with anorexia as well as nausea and vomiting. According to office-based physician surveys, there was no diagnosis reported of anorexia among pediatric patients 15-17 years old.

APPENDIX A:

Table 3.1. Nationally estimated number of patients who received a prescription for dronabinol from U.S. outpatient retail pharmacies, stratified by patient age (0-14, 15-17, 18+ yrs), 2006 - 2015

	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Grand Total	**74,597**	***100.0%***	**74,443**	***100.0%***	**65,704**	***100.0%***	**71,087**	***100.0%***	**80,254**	***100.0%***	**77,505**	***100.0%***	**79,733**	***100.0%***	**85,938**	***100.0%***	**95,660**	***100.0%***	**98,442**	***100.0%***
Age 0 - 17 yrs	673	*0.9%*	656	*0.9%*	736	*1.1%*	794	*1.1%*	1,000	*1.2%*	1,078	*1.4%*	1,109	*1.4%*	1,207	*1.4%*	1,464	*1.5%*	1,710	*1.7%*
Age 0 - 14 yrs	420	*62.4%*	316	*48.1%*	410	*55.7%*	404	*50.9%*	532	*53.2%*	583	*54.1%*	625	*56.4%*	697	*57.8%*	885	*60.4%*	1,005	*58.8%*
Age 15 - 17 yrs	**261**	***38.8%***	**349**	***53.2%***	**335**	***45.6%***	**399**	***50.2%***	**478**	***47.8%***	**516**	***47.9%***	**496**	***44.7%***	**527**	***43.7%***	**606**	***41.4%***	**738**	***43.2%***
Age 18+	73,942	*99.1%*	73,788	*99.1%*	64,989	*98.9%*	70,296	*98.9%*	79,266	*98.8%*	76,450	*98.6%*	78,660	*98.7%*	84,746	*98.6%*	93,986	*98.3%*	95,888	*97.4%*
Unknown Age					2	*0.0%*	11	*0.0%*	9	*0.0%*	11	*0.0%*			48	*0.1%*	560	*0.6%*	1,068	*1.1%*

Source: IMS, Vector One®: Total Patient Tracker. 2006 - 2015. Extracted March 2016. File:TPT 2016-319 Dronabinol by age 3-4-16.xls

**Subtotals may not sum exactly, due to rounding. Patients may have received multiple administrations of drug during the study period and due to aging of patients during the study period, patients may be counted more than once in the individual categories. For this reason, summing is not advisable and will result in overestimates of patient counts.*

Reference ID: 3902745

Table 3.2

Nationally estimated number of dispensed prescriptions by top prescribing specialties for dronabinol from U.S. outpatient retail pharmacies

	Years 2011 - 2015	
	TRx	*Share*
	N	*%*
DRONABINOL	**1,222,821**	***100.0%***
INTERNAL MEDICINE	**216,062**	***17.7%***
ONCOLOGY	**193,852**	***15.9%***
FAMILY PRACTICE	**143,524**	***11.7%***
NURSE PRACTITIONER	**100,302**	***8.2%***
OSTEOPATHIC MEDICINE	**92,119**	***7.5%***
INFECTIOUS DISEASE	**78,183**	***6.4%***
PHYSICIAN ASSISTANT	**47,064**	***3.9%***
GASTROENTEROLOGY	**43,203**	***3.5%***
NEUROLOGY	**42,557**	***3.5%***
ANESTHESIOLOGY	**32,595**	***2.7%***
ALL OTHERS	**233,360**	***19.1%***

Source: IMS National Prescription Audit (NPA). 2011 - 2015. Extracted 2-26-16. File: NPA 2016-319 Dronabinol by MD 2-26-16.xlsx

Table 3.3

Top diagnoses associated with the use* of dronabinol as reported by U.S. office-based physician surveys, stratified by patient age (0-14, 15-17, 18+ yrs)

	Years 2006 - 2015		
	Uses	*Share*	95% Confidence Interval
	N(000)	*%*	(000)
dronabinol	**551**	***100.0%***	**428-674**
Age 0-14 yrs		***no data return***	
Age 15-17 yrs	**3**	***0.6%***	**<0.5-13**
3482 PSEUDOTUMOR CEREBRI	**3**	***100.0%***	**<0.5-13**
Age 18+ yrs	**531**	***96.4%***	**411-652**
7830 ANOREXIA	**106**	***20.0%***	**52-160**
7870 NAUSEA AND VOMITING	**96**	***18.1%***	**45-147**
7837 ADULT FAILURE TO THRIVE	**41**	***7.7%***	**7-75**
1629 MAL NEO BRONCH/LUNG NOS	**37**	***6.9%***	**5-69**
7832 LOSS OF WEIGHT/UNDERWGHT	**32**	***6.0%***	**2-61**
1991 MALIGNANT NEOPLASM NOS	**20**	***3.8%***	**<0.5-44**
1579 MALIG NEO PANCREAS NOS	**19**	***3.7%***	**<0.5-43**
2941 DEMENTIA IN OTH DISEASES	**16**	***3.0%***	**<0.5-37**
7994 CACHEXIA	**15**	***2.9%***	**<0.5-36**
V080 ASYMPTOMATIC HIV STATUS	**14**	***2.6%***	**<0.5-33**
All Others	**135**	***25.4%***	**74-196**
Unknown Age	**17**	***3.0%***	**<0.5-38**
7832 LOSS OF WEIGHT/UNDERWGHT	**7**	***41.6%***	**<0.5-21**
7830 ANOREXIA	**7**	***41.6%***	**<0.5-21**
1629 MAL NEO BRONCH/LUNG NOS	**3**	***16.8%***	**<0.5-12**

Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, 2011 - 2015. Extracted March 2016. File: PDDA 2016-319 Dronabinol by AgeDx4 3-4-16.xls

Drug uses - refer to the mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. "Drug uses" does not necessarily result in prescription being generated but are the projected number of times a given drug was mentioned during an office visit.

Reference ID: 3902745

Appendix B: Drug Use Database Descriptions

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

IMS, National Prescription Audit

The National Prescription Audit (NPA^{TM}) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

PATTY A GREENE
03/15/2016
drug use data cleared 3/15/16 by data vendors

MOHAMED A MOHAMOUD
03/15/2016

GRACE CHAI
03/15/2016

Consult Memo: ICC1500288/ NDA 205525

Date:	February 4, 2016
From:	Sarah Mollo, DAGRID/GHDB
To:	Kathlene Fitzgerald, Lead Reviewer, DAGRID/GHDB
Type of Product:	press in bottle adaptor and oral syringe
Product Name:	Drobinol oral solution
Intended Use:	administration of drobinol oral solution
Sponsor:	Insys Therapeutics, Inc
Consult Review:	Biocompatibility of the Device Constituent

I. Scope of Consult

This consult is a review of the biocompatibility of the patient and fluid contacting components of the press in bottle adaptor and oral syringe.

II. Documents Reviewed

IR Response Toxicity Evaluation Report (b) (4)-SR025A
IR Response Leachable Project Report (b) (4)-M0075
IR Response Leachable Project Report (b) (4)-M0075
Response to Mid Cycle Information Request
IR Response e_1 Summary Memo - November 12, 2015
Response to Filling Review Issues – Device
IR response oral-solution-disp-dev description
Response to IR_(b) (4)
Proposed labeling
Device Description - Dronabinol Oral Solution Dispensing
15t-67759-02-(b) (4)-dispenser
15t-67759-03-15t-67759-04-(b) (4)-dispenser
15t-67759-05-15t-67759-06-(b) (4)-dispenser
15t-67937-02-(b) (4)-adaptor
15t-67937-03-15t-67937-04-(b) (4)-adaptor
15t-67937-05-15t-67937-06-(b) (4)-adaptor
(b) (4)-mid-cycle-info-req

III. Review Summary

All deficiencies have been resolved through interactive review. The sponsor has provided all requested information and test reports. The information within the submission and supplements was adequate to perform a biological evaluation of the devices. The consulting reviewer does not believe that use of the device will result in a toxicological response.

III. Background

Dronabinol Oral Solution is a new formulation of dronabinol intended for oral delivery. Dronabinol Oral Solution contains a synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Dronabinol is an orally active cannabinoid that has many effects on the central nervous system, including sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues and may play a role in mediating the effects of dronabinol and other cannabinoids.

Dronabinol Oral Solution has the same active ingredient, dronabinol, as Marinol® oral capsule and generic dronabinol oral capsule formulations. Inactive ingredients are butylated hydroxyanisole, sucralose, methyl paraben, propyl paraben, dehydrated alcohol (50% w/w), polyethylene glycol400, and propylene glycol.

Dronabinol Oral Solution is packaged in a 30 mL container containing 150 mg dronabinol (5 mg/mL). Dronabinol Oral Solution is co-packaged with an oral dosing syringe marked with the graduations allowing the measurement of prescribed doses.

Proposed Clinical Use

Dronabinol Oral Solution is indicated for the treatment of:
1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in

APPEARS THIS WAY ON ORIGINAL

Indications for use: For the treatment nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.

This product, which was developed under IND 75228 is packaged in a 30 mL container, which is copackaged with a dispenser for oral administration.

VI. Device Description

Oral Dispenser

A clear graduated oral dispenser is provided along with the bottle and press-in bottle adapter for use by the patient in dispensing the product. The oral dispenser will allow the patient to draw the desired dose with accuracy.

The dispenser consists of two parts, a Barrel and a Plunger. The graduation scale is printed on the barrel with a black printing ink. The list of components of the oral dispenser is provided hereafter:

- Barrel:
  - o (b) (4)
  - o
  - o
- Plunger:
  - o (b) (4)
  - o

Press-In Bottle Adaptor

A Clear vented 20 mm press-in bottle adapter is provided along with the oral dispenser for dispensing Dronabinol Oral Solution from the bottle. At the time of first use, a press-in bottle adapter is fitted on to

the bottle and kept there for the entire duration of use. The press-in bottle adapter allows a user to easily draw liquid with the oral dispenser, ensuring accurate dosing while avoiding spills. The adapter fits with the bottle opening so that the original cap can be placed on the bottle. The press-in bottle adapter is manufactured from (b) (4). For commercialization, the press-in bottle adapters are wrapped individually in plastic film.

V. Biocompatibility Review History

The following IRs were sent as part of the "Filing Communication - Filling Review Issues Identified" letter dated August 12, 2015:

FDA Question 9
You stated you performed a chemical stability study in which the dronabinol oral solution was held in the dispensing syringe for 8 hours and the impurity levels were assessed (table 1 on pg. 3 of 3.2.R.4). Provide the data for the leached substances for this test. Alternatively, clarify the use-life of the syringe (i.e., how many times the syringe will be reused and/or over what period of time) and perform a risk assessment the leachables after an incubation period with the drug, consistent with the use-life.

Insys Response
An extractable study was performed using the oral dispensing syringe using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the syringe components for 24 hours (Extractable Report referenced (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose of (b) (4) mL, an analytical evaluation threshold (AET) and reporting threshold were calculated for the amount of extractable per device.

*Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds based on allowable maximum dose of (b) (4) mL (Table 1). Toxicological evaluation showed that PDE for all the compounds th*at can possibly be extracted under reflux conditions were below the acceptable daily intake (ADI) level (Toxicity Evaluation Report (b) (4)-SR025A, Table 2 and Summary Memo dated November 12, 2015).

FDA Question 10
The directions for use state that the opened bottle can be stored for up to 28 days; however, it is unclear if the adapter will be re-used in subsequent bottles of dronabinol oral solution. Clarify the use-life of the adapter and provide leachables/extractables testing using dronabinol as the solvent for the adapter according to the use-life conditions. Alternatively, you can use accelerated conditions (i.e. 50◦ C for 72 hours) to assess the possible leachants/extractants resulting from the interaction between the drug and the adapter.

Insys Response
It is not recommended to re-use the adapter in subsequent bottles of Dronabinol Oral Solution. For each new prescription a new unit of use container is delivered to the patient. The unit of use container includes a 30mL light-resistant bottle containing 150mg of Dronabinol (4.25 mg / 0.85 mL), an oral syringe, and an adapter. It is clearly indicated on the carton submitted in this sequence that the product should be dispensed in this unit-of use container.

An extractable study was performed using the press-in bottle adapter using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the bottle adapter for 24 hours (Extractable Report (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose an analytical evaluation threshold (AET) and reporting threshold was calculated for the amount of extractable per device.

Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds. Toxicological evaluation showed that PDE for all the compounds that can possibly be extracted under reflux conditions was below the acceptable daily intake (ADI) level. Refer to Toxicity Evaluation Report (b) (4)-SR025A, Table 1, Table 2 and Summary Memo dated November 12, 2015 for detailed information.

The targets for leachables were identified based on the extractable characterization study. The leachables analysis was performed on drug product sample that was held in the presence of bottle adapter for 28 days at ambient conditions. The bottle was placed in horizontal orientation to provide constant contact of bottle adapter with drug product solution. None of the potential leachables were detected in this sample (Leachable Report (b) (4)-M0075). Based on the results of leachable study the bottle adapter can be in contact with the drug product during its use over 28 days at ambient conditions of storage.

FDA Question 11

You provided an USP <661> testing summary for the syringe barrel and plunger as well as the bottle adapter; however, the information in this summary was limited. Provide your test protocol(s), including but not limited to the specific solvents used, extraction time, extraction ratio and extraction conditions. Provide an evaluation of your results including an explanation as to why the amount (mg) of nonvolatiles extracted does not present a safety concern to the patient.

Insys Response

In the previous response dated August 28, 2015, Insys provided experimental details of USP <661> testing. This is a gravimetric test and the limits have been developed by USP in order to assess suitability of material being used in the manufacture of components used.

For the evaluation of safety of any leachables that may be present due to exposure to syringe and bottle adapter, Insys conducted extractable characterization and leachable identification studies as outlined in response to Questions 9 and 10. A leachables study showed that only one compound (b) (4) was observed above the analytical evaluation threshold for the syringe sample and the amount present is well below the acceptable daily intake. The bottle adapter did not show any leachables present above AET. Based on this analysis leachables expected to be present due to syringe and bottle adapter contact are well below any toxicity concern.

The following IRs were sent as part of the Mid Cycle Information Request letter dated November 17, 2015:

FDA Question 1

The information describing the nature and duration of patient contact of the oral dispenser and press-in adapter device components could not be located within the submission. Please provide a description of the category and duration of contact of each device component (i.e. adapter and syringe).

Insys Response
Category of the device is Surface Device. Based on the review of the tapes of the label comprehension study submitted on June 01, 2015, the total amount of time spent contacting the adapter or syringe was approximately five minutes. Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h). Please refer to the report of the label comprehension study, submitted on June 01, 2015, for details on this study.

FDA Question 2
Additionally, we were unable to locate an evaluation of the biocompatibility of the oral dispenser and press-in adapter device components. Please provide the appropriate biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. Please provide the test summaries, test method (including sample preparation and acceptance criteria), full test reports, and an analysis of the results.

Insys Response
Please find the accompanying letter from the manufacturer of the adapters and syringes attesting these products are currently being used for OTC, Rx, and Oral Liquid applications. They are Class I Medical Devices and are exempt from 510K Pre-Market Submission requirements. The manufacturer, (b) (4) *has provided USP Class VI testing for the* (b) (4) *used in the manufacture of barrel for oral dispenser.*

As Dronabinol Oral Solution is now classified as a combination product, Insys will initiated the biocompatibility study with the oral dispenser and bottle adapter and anticipate submission of results to FDA by middle of January 2016.

Updated Insys Response
In response to this question, Insys initiated biocompatibility studies with the oral dispenser and bottle adapter.

Based on the FDA draft guidance, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" issued on April 23, 2013, the oral dispenser and adapter are both classified as surface devices and have limited contact. Biocompatibility testing needed are Cytotoxicity, Sensitization, and Intracutaneous Reactivity. These tests were performed by contract testing lab (b) (4) *under pre-approved protocols and results are summarized below. Devices meet the requirement of biocompatibility as defined in the guidance. Please note, section 3.2.R.4 was updated to describe biocompatibility study results as well.*

1) Cytotoxicity: The test articles, Oral Dispenser and Adapter, were evaluated separately for potential cytotoxic effects using an in vitro mammalian cell culture test. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A single preparation of the test article was extracted in single strength Minimum Essential Medium (lX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly extracted. Triplicate mono layers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% C02 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration. The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test because the

grade was less than a grade 2 (mild reactivity). Details of the methodology followed and test results are in the attached reports 15T_67759_02 (dispenser) and 15T_67937_02 (adaptor).

2) Sensitization: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices -Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test. Details of the methodology followed and test results are in the attached reports 15T_67759_05/15T_67759_06 (dispenser) and 15T_67937_05/15T_67937_06 (adaptor).

3) Intracutaneous Reactivity: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively. Details of the methodology followed and test results are in the attached reports 15T_67759_03/15T_67759_04 (dispenser) and 15T_67937_03/15T_67937_04

VI. Biocompatibility Summary

The following response was provided by the sponsor for duration of patient contact:

Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h).

The oral syringe and press in bottle adaptor will come into contact with patient skin (limited contact). However, the device will also come into contact with the drug, which will then be administered orally. Therefore, the sponsor was requested to perform a chemical characterization and risk assessment to address the systemic toxicity of possible leachables from the device.

Biocompatibility testing provided by the sponsor

The sponsor conducted the following biocompatibility testing on the oral syringe and press-in bottle adaptor:

a. *In vitro* cytotoxicity
b. Sensitization;
c. Intracutaneous reactivity;

The biocompatibility testing was conducted by (b) (4) (b) (4) declared that the biocompatibility testing was conducted in accordance with 21 CFR Part 58. The extraction conditions and test methods were performed in accordance with 10993-5 and 10993-10. The results demonstrated that the devices were: non-cytotoxic, non-sensitizing, and non-irritating.

Extractables and leachables Studies

Extractable Report Summary

The samples were characterized for volatile, semi-volatile, and non-volatile/polar organic extractables and inorganic extractables. Volatile compounds and (b) (4) *were characterized using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionization (EI), and semi-volatile compounds were characterized using gas chromatography-mass spectrometry (GC-MS) with EI. Nonvolatile/ polar compounds were characterized using high performance liquid chromatography-ultraviolet-mass spectrometry (HPLC-UV-MS) with positive and negative atmospheric pressure chemical ionization (APCI). Inorganic compounds were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS).*

Volatile compounds were analyzed directly by HS GC-MS from the headspace of the samples in sealed vials incubated at an elevated temperature. Semi-volatile and nonvolatile/ polar extractables were generated for the adapter, barrel, and plunger components by 24-hour reflux extraction of the samples in 50:50 water:ethanol (H2O:ethanol) and isopropanol (IPA). The IPA extracts were not semi-quantitated (b) (4) *and were only generated to aid in the peak identification for the extracts which do mimic the drug product.*

Inorganic extractables were generated for the adapter, barrel, and plunger by maceration in dilute nitric acid for 24 hours at 60 °C. The semi-volatile extractables were profiled by GC-MS, and non-volatile/polar extractables were analyzed by HPLCUV-MS. The inorganic extractables were analyzed by ICP-MS. The reporting threshold was (b) (4) *ppm for the HS GC-MS analysis, and the Analytical Evaluation Threshold (AET) was applied in the GC-MS, HPLC-UV-MS, and ICP-MS analyses.*

In the HS GC-MS analysis, (b) (4) *were observed above the reporting threshold for the adapter, barrel, and plunger samples.* (b) (4) *were also observed above* (b) (4) *ppm for the barrel sample.*

In the GC-MS analysis, (b) (4) *were observed above the AET for the barrel 50:50 H2O:ethanol extract. No peaks were observed above the AET for the adapter and the plunger extracts.*

In the LC-MS analysis, (b) (4) *was observed above the AET or the barrel 50:50 H2O:ethanol extract. No peaks were observed above the AET for the adapter and the plunger extracts.*

Leachables Report Summary

[redacted] *conducted an in-use leachables assessment for Dronabinol Oral Solution drug product in contact with transient container systems consisting of a press-in bottle adapter and dispensing syringe for Insys Therapeutics (Customer). The migration study was conducted for 28 days at room temperature for the press-in bottle adapter and for 8 hours at room temperature for the syringe.*

The samples were screened for volatile, semi-volatile, and non-volatile organic leachables and inorganic leachables. Volatile compounds and [redacted] *were characterized using headspace gas chromatography-mass spectrometry (HS GC-MS) with electron ionization (EI), and semi-volatile compounds were characterized using gas chromatography-mass spectrometry (GC-MS) with EI. Non-volatile/polar compounds were identified using high performance liquid chromatography-ultraviolet-mass spectrometry (HPLC-UV-MS) with positive and negative atmospheric pressure chemical ionization (APCI). Inorganic compounds were analyzed using inductively coupled plasma-mass spectrometry (ICP-MS).*

Volatile leachables were prepared by combining the drug product with methanol to adulterate the product. Semi-volatile and non-volatile/polar leachables were prepared by liquid-liquid extraction of the drug product with methylene chloride. Inorganic leachables were prepared by microwave extraction in a concentrated hydrochloric acid and 30% hydrogen peroxide mixture. The Analytical Evaluation Threshold (AET) was applied in the HS GC-MS, GC-MS, HPLC-UV-MS, and ICP-MS analyses.

For the HS GC-MS analysis, no non-control related peaks were observed above the AET for the adapter and syringe migration samples.

For the GC-MS analysis, [redacted] *was observed above the AET in the syringe migration sample. No peaks were observed above the reporting threshold in the adapter migration sample.*

No non-control related peaks were observed above the reporting threshold for the migration samples, for the HPLC-UV-MS analysis.

For the metals analysis, no elements were observed above the reporting threshold for the migration samples.

A spiking study was conducted for all analyses to determine if compound classes commonly observed in plastics could be observed by the screening methods in the presence of the drug product matrix at the AET concentration. All targets were observed by all screening methods with the exception of [redacted] *by HS GC-MS analysis.*

Reviewer Comment

The extraction methods used for the extractables and leachables studies are acceptable. The leachable migration study of 28 days for adaptor; and the 8 hours for the syringe is consistent with conditions of use. Use of 50:50 water:ethanol (H2O:ethanol) and isopropanol (IPA) as solvents is acceptable. The IPA extracts were not semi-quantitated [redacted] and were only generated to aid in the peak identification for the extracts which do mimic the drug product. Quantitation of the 50:50 ethanol water solvent only is acceptable, as the sponsor states that is representative of the Dronabinol Oral Solution formulation.

The analytical chemistry approach used to identify and quantify extractables appears to be appropriate. A number of extractable compounds were identified and the ADI value for each of the extractables present

over the AET was calculated correctly by the sponsor either from toxicity data in the literature or by the use of the TTC approach (see below for a summary of the toxicological risk assessment).

Toxicological Risk Assessment

The extractables specified in Table 1 below were identified as potential leachables of a pharmaceutical drug product. Table 1 provides the Potential Daily Exposure (PDE) to these extractables with clinical use of the inhalation drug product. Table 1 also indicates the number of times the Acceptable Daily Intake (ADI) or Threshold of Toxicological Concern (TTC) exceeds the PDE for adults (60-kg mean bw) and children (11-kg mean bw), and the associated human health risk assessment (safe or unsafe) for each specified extractable. The risk assessment referenced the data/resports used to develop the ADI or TTC values and summarized this information in tables 3a and 3b.

If possible, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) approach was used to compute an ADI based on uncertainty factor (UF) multiples of 10 and mean body weight (bw). The calculated ADI is then compared to the PDE to estimate the human health risk. TTC values are established as needed *via* Toxtree, for estimation of toxicity using a decision tree approach. The TTC approach is applied for cases where a reliable ADI cannot be established from relevant scientific literature. The specified extractables of the inhalation drug product have been determined to be safe for human exposure during clinical use of the product, based on the specified PDEs.

The ratios of ADI/PDE (or TTC/PDE) for the extractables range from (b) (4) and from (b) (4) for adults and children, respectively. The term "safe" is applied whenever the PDE is below the ADI or TTC (the ADI/PDE or TTC/PDE ratio >1). The ratios of ADI/PDE or TTC/ADI are representative of margins of human safety. Determination of safety where ADI/PDE or TTC/PDE ratios < 1 are made on a case-by-case basis. See footnote to Table 1.

The reference dose (RfD in mg/kg bw/day) is defined as an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of significant health effects during a lifetime. The RfD is determined by use of the following equation: RfD = (NOAEL or LOAEL)/(UF), where the NOAEL is the "no observed adverse effect level" and LOAEL is the "lowest observed adverse effect level". UF is called the uncertainty factor. UFs are products of 10 that are used to lower the NOAEL or LOAEL due to uncertainty in the critical study used to determine the LOAEL or NOAEL. The following criteria are used to calculate UFs:

(i.) Use one factor of ten to account for the variation in sensitivity to the chemical among members of the human population.
(ii.) Use one factor of ten to account for the uncertainty of extrapolating data from animal studies to humans.
(iii.) Use one factor of ten to account for use of data from a subchronic study (less than 90 days).
(iv.) Use one factor of ten when the LOAEL is used instead of the NOAEL.

Acceptable daily intake (ADI) is calculated from the Reference Dose (RfD)
For adults: ADI (mg/day) = (RfD in mg/kg bw/day) x 60-kg mean Body Weight
For children: ADI (mg/day) = (RfD in mg/kg bw/day) x 11-kg mean Body Weight

Reviewer comment
The uncertainty factors used by the sponsor were conservative. The method used to calculate the ADI is acceptable.

Table 1. Extractable, CAS Number, Acceptable Daily Intake (ADI), Potential Daily Exposure (PDE), the number of times the Acceptable Daily Intake (ADI) or Threshold of Toxicological Concern (TTC) exceeds the PDE for adults (60-kg bw) and children (11-kg bw), and the Human Safety Assessment.

Extractable	CAS No.	ADI or TTC [1] [µg/day]	PDE [µg/day]	ADI/PDE [2] or TTC/PDE	Human Safety Assessment
(b) (4)					Safe
					Safe
					Safe
					Safe
					Safe

(b) (4)	
	See comment below*
	Safe
	Safe
	Safe
	Safe

[1] Values in this column are for ADIs unless otherwise noted.

[2] Refer to Tables 2, 3a and 3b for details.

(b) (4)

Reviewer Comment

In most cases, the calculated ADI values of the compounds extracted from the device are well above the estimated daily exposure values for the compounds, yielding Margin of Safety (MOS) values >1. However, the MOS for one compound, (b) (4) (see table below).

(b) (4)

The ADI calculated for this compound is based on NOAEL of (b) (4) mg/kg/day and a modifying factor of 1000, with factors of 10 each used to account for inter-individual variability, interspecies differences in potency, and the use of a NOAEL from a short-term toxicity study. Since use of the drug product is not likely to occur over a lifetime, the use of the UF of 10 for short-term toxicity data yields a modifying factor (MF) of 1000 (10 x 10 x 10) that is probably overly conservative for this device. An alternate approach would be to base the MF simply on the product of the UFs to account for inter-individual variability (10) and interspecies differences in potency (10), resulting in a MF of 100 and an ADI of (b) (4) mg/kg/day or (b) (4) µg/day for a 60 kg adult and (b) (4) µg/day for a 10 kg child. Both of these ADI values are greater than the dose of the compound extracted from the device, resulting in a MOS > 1.

Reviewer comment

The ADI values for each of the compounds were derived using data from noncancer endpoints in toxicity studies or TTC values intended to be protective for noncancer endpoints. The ADI values used in the risk

assessment were derive ADI values that are protective for noncancer and cancer-based effects. Dr. Ronald Brown (toxicologist, OCEL) provided the following rationale for the acceptability of this approach:

The ADI values for each of the compounds were derived using data from noncancer endpoints in toxicity studies or TTC values intended to be protective for noncancer endpoints. However, if the device can be used for a prolonged period, then it is important to derive TI values that are protective for both cancer-based and noncancer effects. Screening of the extractables for potential carcinogenicity using the Toxtree program resulted in identification of two compounds with structural alerts for genotoxic carcinogenicity and mutagenicity in the Ames test, (b) (4). A search of the CCRIS database reveals that (b) (4) has been tested in several strains of *S. typhimurium* in the Ames test and the results negative. (b) (4) has been tested in multiple genotoxicity test systems and has shown negative results in the Ames test, *in vitro* micronucleus, *in vitro* chromosomal aberrations, and unscheduled DNA synthesis, but positive results when tested in CHO V79 cells. Although positive results were reported in this assay, this compound has undergone extensive *in vitro* genotoxicity testing in a battery of assays and the weight of evidence suggests that the compounds is not genotoxic. Therefore, despite the presence of a structural alert for carcinogenicity and mutagenicity, the (b) (4) compounds extracted from the device are not likely to be genotoxic. Consequently, the ADI values used by the submitter in the risk assessment are appropriate. Since none of the compounds extracted from the device are likely to be mutagenic, no additional genotoxicity testing is needed to assess the carcinogenic potential of extractables released from the device.

Reviewer Comment
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.

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

/s/

MAUREEN D DEWEY
03/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 24, 2016
From: Kathleen FitzGerald, Nurse consultant WO66, RM2510
CDRH/ODE/DAGRID/GHDB
To: Maureen Dewey CDER/OND/ODEIII/DGIEP
Subject: ICC1500288, CDRH/ODE Oral Dispenser and Press-In Adapter device components review for NDA 205525 Dronabinol Oral Solution

1. Issue/Request from CDER:
The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding the oral syringe in NDA 205525 Dronabinol Oral Solution.
This product, which was developed under IND 75228 is packaged in a 30 mL container, which is copackaged with a dispenser for oral administration.
This is being filed as a 505(b)(2) application with NDA 018651 for Marinol® (dronabinol) capsules as the reference drug. Dronabinol Oral Solution is indicated for the (b) (4) nausea and vomiting associated with cancer chemotherapy (b) (4).
Please provide expertise on all matters related to manufacturing aspects of syringes and Human Factor studies.
This submission can be accessed through the following link:
\CDSESUB1\evsprod\NDA205525\205525.enx

This review is limited to the oral dispenser and press-in adapter used in NDA 205525.

CDER is reviewing the primary container 30 mL clear amber color (b) (4) glass bottle that contains Dronabinol Oral Solution. The bottle closure is a 20 mm child-resistant cap with a Teflon coated liner.

DMEPA will be reviewing the Human Factors portion.

Sarah Mollo, CDRH/ODE/GHDB, reviewed the biocompatibility data and test reports for the Oral Dispenser and Press-In Adapter.

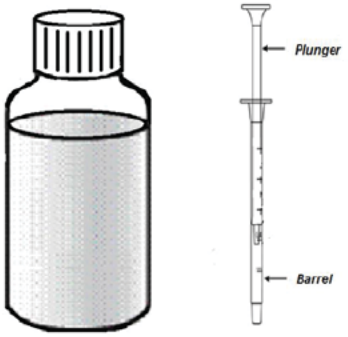
2. **Device Description:**
Product Name: Dronabinol Oral Solution

Reference ID: 3899997

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.

Container Closure System Description:
Dronabinol Oral Solution is packaged in a multi-dose container closure system. Standard pharmaceutical packaging materials were selected for the product.
The primary container is 30 mL clear amber color (b) (4) glass bottle. The bottle closure is a 20 mm child-resistant cap with a Teflon coated liner.
Refer to Section 3.2.P.7.1 for detailed technical and regulatory information for the bottle and child-resistant cap including materials of construction, drawings and controls.
The container is wrapped with a PVC body band to provide tamper evidence and packaged in a suitably sized carton along with a graduated oral dispenser.

A clear graduated oral dispenser and press-in bottle adapter are provided in the carton along with drug product and package insert. At the time of first use, the press-in bottle adapter is fitted on to the bottle that allows the patient to draw the product using an oral dispenser with ease.
Markings (b) (4) are printed on the (b) (4) dispenser, same as the (b) (4) oral dispenser that was used in the pivotal clinical trial INS-12-015. Use of the oral dispenser was validated in a label comprehension study. Refer to Section 3.2.R.4 for detailed technical and regulatory information for the graduated oral dispenser and press-in bottle adapter including materials of construction, drawings and controls.



Oral Dispenser: A clear graduated oral dispenser is provided along with the bottle and press-in bottle adapter for use by the patient in dispensing the product. The oral dispenser will allow the patient to draw the desired dose with accuracy. The dispenser consists of two parts, a barrel and a plunger. Graduation scale is printed on the barrel with black printing ink. (b) (4) .

- Barrel

Reference ID: 3899997

- [redacted]
- Plunger [redacted]

Press-in Bottle Adapter: A clear vented 20 mm press-in bottle adapter is provided along with the oral dispenser for dispensing Dronabinol Oral Solution from the bottle. At the time of first use, a press-in adapter is fitted on to the bottle and kept there for the entire duration of use. The press-in bottle adapter allows the user to draw the liquid medication with the oral dispenser.
The press-in bottle adapter is manufactured from [redacted].

Regulatory fact sheet
[redacted] confirms that [redacted], as manufactured and shipped from [redacted] facilities, can be used in complying with Title 21 of the Code of Federal Regulations, CFR, per the conditions below:
[redacted] confirms that [redacted] is produced with raw materials and operating practices that would not render the [redacted] unsafe or unsuitable for contact with food within the meaning of Sections 402 and 409 of the Federal Food, Drug, and Cosmetic Act and its implementing regulations including the Good Manufacturing Practice regulation, 21 CFR §174.5 "General Provisions applicable to indirect food additives".

3. Documents Reviewed:
- ICC1500288 consult request from CDER
- NDA 205525 application.
- LOA to review DMF [redacted]
- DMF [redacted] for the oral dispenser and press-in adapter by [redacted].
- The Applicant's response to CDRH's additional information request dated August 10, 2015.
- The Applicant's response to CDRH's biocompatibility additional information request November 2015 and January 2016.

4. CDRH Review and Comments:
This review was limited to the proposed oral dispenser and press-in adapter combination product presentation in NDA 205525.

Reference ID: 3899997

DMF [redacted] for the oral dispenser and press-in adapter by [redacted] DMF [redacted] contains complete device materials information.

- **Performance Tests in NDA 205525 for the oral dispenser and press-in adapter.**

Test name: Dose Accuracy: Accuracy of Dronabinol Oral Solution Dispensing with the oral dispenser proposed for commercialization

Results:

- The visual inspection of [redacted] syringes showed no physical defects on the syringes used in the study. Accuracy of dispensing data indicates that the error was no more than 1.464% away from target volume of 0.85 mL, individual dose dispensed by [redacted] Syringe was not greater than 2.5 % of "Target volume".
- Accuracy of Syringe conforms to 2011 U.S.P 34/NF 29, Teaspoon, Chapter <1221> specification, and 2014 U.S.P 37/NF 32, "Deliverable Volume", Chapter <698>. "Deliverable Volume". Within the range of [redacted]%.

Conclusion:

[redacted] oral dispenser is suitable for Dronabinol Oral Solution and allows accurate dispensing of the product.

Test Name: Accessibility of Dosing and Compatibility between Oral Dispenser and Press-In Bottle Adaptor.

Results:

Visual inspection Oral Dispenser suggests that there were no physical defects on the oral dispensers used the study.

Accessibility of dosing/Dispensing test demonstrated that 65 to 67 accurate doses of 0.425mL and 33 to 34 accurate doses of 0.85 mL can be delivered using [redacted] Oral Dispenser and press in bottle adapter.

No compatibility issues were observed during the entire study while withdrawing doses using press in adapter and [redacted] Oral Dispenser.

Conclusion:

Dispensing data indicates that a minimum of 65 doses of 0.425mL 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.

- **Cleaning Instructions for the oral dispenser:** In the instructions for use: Remove the plunger from the syringe barrel. Rinse the syringe barrel and plunger with warm [redacted] water after each use and let air dry. When the syringe barrel and plunger are dry, put the plunger back into the syringe barrel for the next use.

[redacted]

Previous deficiencies and information request with Applicant's Responses:

- **Information request from the CDRH/ODE/GHDB lead consult review of the oral dispenser and press-in adapter on August 10, 2015:**

1. Please provide a sample of the oral dispenser and press-in adapter for our review.

Reference ID: 3899997

Applicant's Response: Two samples of the proposed product, including the: packaging, multi-dose container, graduated oral dispenser/syringe, and press-in bottle adapter for dose dispensing accompany this response.

CDRH's Response: The Applicant provided a sample of the device components. All the components are compatible and function as intended and per the instructions for use.

2. In NDA 205525 you have provided limited device information for the oral dispenser and press-in adapter. You have referenced DMF (b) (4) for additional information. The information obtained in DMF (b) (4) for the oral dispenser and press-in adapter is the materials of construction for these devices. I was not able to locate performance bench test reports in the DMF and only one bench test report for dose accuracy in NDA 205525. Please provide complete functionality performance bench test reports for the oral dispenser and press-in adapter in NDA 205525. As well as performance test reports to demonstrate compatibility of the oral dispenser and press-in adapter and how many times the adapter can be accessed by the oral dispenser.

Applicant's Response: To address the FDA's request to conduct bench studies on the functionality performance of the syringe and adapter combination, we performed a bench study. A description of this study and its results are included in the report RD.0002 accompanying this submission. An updated section 3.2.R.4 is also provided.
Please note, for DMF completeness, (b) (4) also provided a Failure Modes and Effects Analysis (FMEA) for the manufacturing process of the device. We enclose this for your information.

CDRH's Response: The Applicant provided 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.

- **Information request from the CDRH/ODE/GHDB Biocompatibility consult review of the oral dispenser and press-in adapter:**

1. You stated you performed a chemical stability study in which the Dronabinol Oral Solution was held in the dispensing syringe for 8 hours and the impurity levels were assessed (table 1 on pg. 3 of 3.2.R.4). The sponsor should provide the data for the leached substances for this test. Alternatively, the sponsor can clarify the use-life of the syringe (ie. how many times the syringe will be reused and/or over what period of time) and perform a risk assessment of the leachables after an incubation period with the drug, consistent with the use-life.

Applicant's Response: *An extractable study was performed using the oral dispensing syringe using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the syringe components for 24 hours (Extractable Report referenced (b) (4)-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose of (b) (4) mL, an analytical evaluation threshold (AET) and reporting threshold were calculated for the amount of extractable per device.*

Reference ID: 3899997

Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds based on allowable maximum dose of (b) (4) *mL (Table 1). Toxicological evaluation showed that PDE for all the compounds th*at can possibly be extracted under reflux conditions were below the acceptable daily intake (ADI) level (Toxicity Evaluation Report (b) (4)-SR025A, Table 2 and Summary Memo dated November 12, 2015).

CDRH's Response: The Sponsor's response is adequate.

2. The directions for use state that the opened bottle can be stored for up to 28 days; however, it is unclear if the adapter will be re-used in subsequent bottles of Dronabinol. The sponsor should clarify the use-life of the adapter and provide leachables/extractables testing using Dronabinol as the solvent for the adapter according to the use-life conditions. Alternatively, the sponsor can use accelerated conditions (ie. 50° C for 72 hours) to assess the possible leachants/extractants resulting from the interaction between the drug and the adapter.

Applicant's Response: *It is not recommended to re-use the adapter in subsequent bottles of Dronabinol Oral Solution. For each new prescription a new unit of use container is delivered to the patient. The unit of use container includes a 30mL light-resistant bottle containing 150mg of Dronabinol (4.25 mg / 0.85 mL), an oral syringe, and an adapter. It is clearly indicated on the carton submitted in this sequence that the product should be dispensed in this unit-of use container.*
An extractable study was performed using the press-in bottle adapter using 50:50 ethanol:water and isopropanol as extracting solvent by refluxing the bottle adapter for 24 hours (Extractable Report (b) (4) *-M0074). Extract obtained using 50:50 ethanol water is representative of the Dronabinol Oral Solution formulation. The extractables were characterized by various techniques such as headspace GC-MS (volatile extractables), GC-MS (semi-volatile extractables), HPLC-UV-MS (non-volatile polar extractables) and ICP-MS (metals extractables). Based on the maximum daily dose an analytical evaluation threshold (AET) and reporting threshold was calculated for the amount of extractable per device.*
Extractable compounds identified were subjected to toxicological evaluation. Potential daily exposure (PDE) amount was calculated for the extractable compounds. Toxicological evaluation showed that PDE for all the compounds that can possibly be extracted under reflux conditions was below the acceptable daily intake (ADI) level. Refer to Toxicity Evaluation Report (b) (4) *-SR025A, Table 1, Table 2 and Summary Memo dated November 12, 2015 for detailed information.*

The targets for leachables were identified based on the extractable characterization study. The leachables analysis was performed on drug product sample that was held in the presence of bottle adapter for 28 days at ambient conditions. The bottle was placed in horizontal orientation to provide constant contact of bottle adapter with drug product solution. None of the potential leachables were detected in this sample (Leachable Report (b) (4)-M0075). Based on the results of leachable study the bottle adapter can APPEARS THIS WAY ON ORIGINAL

CDRH's Response: The Sponsor's response is adequate.

3. The sponsor has provided an USP <661> testing summary for the syringe barrel and plunger as well as the bottle adapter; however, the information in this summary was limited. The sponsor should provide their test protocol(s), including but not limited to the specific solvents used, extraction time, extraction ratio and extraction conditions. They should also provide an evaluation

Reference ID: 3899997

of their results including an explanation as to why the amount (mg) of nonvolatiles extracted does not present a safety concern to the patient.

Applicant's Response: *In the previous response dated August 28, 2015, Insys provided experimental details of USP <661> testing. This is a gravimetric test and the limits have been developed by USP in order to assess suitability of material being used in the manufacture of components used.*
For the evaluation of safety of any leachables that may be present due to exposure to syringe and bottle adapter, Insys conducted extractable characterization and leachable identification studies as outlined in response to Questions 9 and 10. A leachables study showed that only one compound (b) (4) *was observed above the analytical evaluation threshold for the syringe sample and the amount present is well below the acceptable daily intake. The bottle adapter did not show any leachables present above AET. Based on this analysis leachables expected to be present due to syringe and bottle adapter contact are well below any toxicity concern.*

CDRH's Response: The Sponsor's response is adequate. This deficiency has been resolved.

4. The sponsor should clarify if the adapter and/or syringe were sterilized.

Applicant's Response: The adapter and syringe are not sterilized as for the oral administration sterilization is not required.

CDRH's Response: The Sponsor's response is adequate.

5. Mid-Cycle Additional Information CDRH/ODE request for the Oral Dispenser and Press-In Adapter:

The Applicant has adequately responded to the previous additional information requests. They have stated that the will be providing the requested biocompatibility test reports around November 9, 2015. During the review of the Applicant's response two additional deficiencies were noted.

Please provide the following to the Applicant regarding the Oral Dispenser and Press-In Adapter:

1. The information describing the nature and duration of patient contact of the Oral Dispenser and Press-In Adapter device components could not be located within the submission. Please provide a description of the category and duration of contact of each device component (ie. adapter and syringe).

   Applicant's Response: *Category of the device is Surface Device. Based on the review of the tapes of the label comprehension study submitted on June 01, 2015, the total amount of time spent contacting the adapter or syringe was approximately five minutes. Dosing twice daily would amount to 10 minutes total. The bottle should last 28 days, which would result in approximately 4 ½ hours. According to the Use of International Standard ISO-10993, this amount of time would be classified as limited (≤ 24 h). Please refer to the report of the label comprehension study, submitted on June 01, 2015, for details on this study.*

Reference ID: 3899997

2. Additionally, the reviewer was unable to locate an evaluation of the biocompatibility of the Oral Dispenser and Press-In Adapter device components. Please provide the appropriate biocompatibility testing commensurate with the level of patient contact according to ISO 10993, Biological Evaluation of Medical devices Part 1: Evaluation and Testing. Please provide the test summaries, test method (including sample preparation and acceptance criteria), full test reports, and an analysis of the results.

Applicant's Response: *Please find the accompanying letter from the manufacturer of the adapters and syringes attesting these products are currently being used for OTC, Rx, and Oral Liquid applications. They are Class I Medical Devices and are exempt from 510K Pre-Market Submission requirements. The manufacturer,* (b) (4) *has provided USP Class VI testing for the* (b) (4) *used in the manufacture of barrel for oral dispenser.*
As Dronabinol Oral Solution is now classified as a combination product, Insys will initiated the biocompatibility study with the oral dispenser and bottle adapter and anticipate submission of results to FDA by middle of January 2016.
Updated Insys Response
In response to this question, Insys initiated biocompatibility studies with the oral dispenser and bottle adapter.
Based on the FDA draft guidance, Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" issued on April 23, 2013, the oral dispenser and adapter are both classified as surface devices and have limited contact. Biocompatibility testing needed are Cytotoxicity, Sensitization, and Intracutaneous Reactivity. These tests were performed by contract testing lab (b) (4) *under pre-approved protocols and results are summarized below. Devices meet the requirement of biocompatibility as defined in the guidance. Please note, section 3.2.R.4 was updated to describe biocompatibility study results as well.*
1) Cytotoxicity: The test articles, Oral Dispenser and Adapter, were evaluated separately for potential cytotoxic effects using an in vitro mammalian cell culture test. This study was conducted following the guidelines of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A single preparation of the test article was extracted in single strength Minimum Essential Medium (lX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly extracted. Triplicate mono layers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% C02 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration. The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test because the
grade was less than a grade 2 (mild reactivity). Details of the methodology followed and test results are in the attached reports 15T_67759_02 (dispenser) and 15T_67937_02 (adaptor).
2) Sensitization: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices -Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP and sesame oil, NF. Each extract was intradermally injected and occlusively patched to ten test guinea pigs (per extract). The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs (per vehicle). Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article

Reference ID: 3899997

was not considered a sensitizer in the guinea pig maximization test. Details of the methodology followed and test results are in the attached reports 15T_67759_05/15T_67759_06 (dispenser) and 15T_67937_05/15T_67937_06 (adaptor). 3) Intracutaneous Reactivity: The test articles, Oral Dispenser and Adapter, were evaluated separately for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A 0.2 mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. The test article met the requirements of the test since the difference between each test article extract overall mean score and corresponding control extract overall mean score was 0.0 and 0.2 for the SC and SO test article extracts, respectively. Details of the methodology followed and test results are in the attached reports 15T_67759_03/15T_67759_04 (dispenser) and 15T_67937_03/15T_67937_04

CDRH Biocompatibility Review Summary: All deficiencies have been resolved through interactive review. The sponsor has provided all requested information and test reports. The information within the submission and supplements was adequate to perform a biological evaluation of the devices. The consulting reviewer does not believe that use of the device will result in a toxicological response.
CDRH Final Recommendation: The Applicant has adequately addressed all CDRH deficiencies.

Please contact Kathleen FitzGerald at (301) 796 – 6292, if you have any questions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Kathleen E. Fitzgerald -A Digitally signed by Kathleen E. Fitzgerald -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -A Date: 2016.02.24 11:43:08 -05'00'
Team-Leader Sign-Off	
Branch Chief Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.02.29 07:56:50 -05'00'
Division Sign-Off	

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/s/

MAUREEN D DEWEY
03/10/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality
Respiratory, ENT, General Hospital, and Ophthalmic Devices Branch

DATE:	October 26, 2015 **Update: February 18, 2016**
TO:	Maureen Dewey, CDER/OND/ODEIII/DGIEP, WO22 RM5232 Maureen.Dewey@fda.hhs.gov Julie G. Beitz, CDER/OND/ODEIII/DGIEP, WO22 RM5214 Julie.Beitz@fda.hhs.gov Office of combination products at combination@fda.gov
Through:	For Francisco Vicenty, Branch Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3425
From:	Bleta Vuniqi, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429
Applicant:	Insys Therapeutics, Inc. 1333 South Spectrum Boulevard, Suite 100 Chandler, AZ, 85286 FEI# 3010878756
Application #	NDA 205525
Product Name:	Dronabinol Oral Solution
Consult Instructions:	Evaluate the Dronabinol Oral Solution documents provided by the applicant on quality system requirement 21 CFR 820, and determine if an inspection of the manufacturing facilities is required. **Update: evaluate the firm's response to the deficiencies**

Viky Verna -A
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Date: 2016.03.01 13:36:00 -05'00'

sent on October 26, 2015

Background:

The Office of Compliance at CDRH received a consult request from CDER to evaluate NDA 205525 covering the medical device constituents of the combination product, and determine if an inspection of the manufacturing facilities is warranted.

Combination Product Description:

Dronabinol Oral Solution is supplied as a single size multi-dose container comprised of a 30 mL glass bottle with a 20-mm child-resistance cap. For tamper evidence, the bottle is wrapped with a PVC body band, and packaged in a suitable size carton along with a graduated oral dispenser for dose dispensing.

The proposed indication is for the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatments and anorexia associated with weight loss in patients with AIDS.



Table 1: 30 mL Bottle Control Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Overflow volume	Complies	Volumetric
Closure fit	Fits with the 20 mm child-resistant cap	Visual
Material verification	Clear Amber (b) (4) Glass	Visual verification and supplier CoA verification

Table 2: Child Resistant Cap Specifications and Analytical Procedures

Test	Acceptance Criteria	Procedure
General Appearance	Complies	Visual
Dimensions (overall height, overall and internal diameter, etc.)	Complies with Supplier Technical Drawing	Caliper Measurement
Outer cap and inner shell material/color verification	Complies	Visual verification and CoA verification
Closure fit	Fits with the 30mL glass bottle	Visual
Identification of Teflon layer[a]	IR spectrum obtained for the sample has similar maxima and minima of IR absorption as the reference spectrum[b]	IR Spectroscopy

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following deficiencies were found:

1. There was no information available for review regarding compliance with 21 CFR 820.20 (Management Controls) 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (Corrective and Preventive Action).

2. Based on the information provided, it could not be determined which facility was responsible for developing the design specifications of the device constituent part, and which facility is maintaining the design history file.

3. The description of the manufacturing activities of the finished combination product was not provided. The application did not include information on how and where the finished combination product would be assembled. No information was provided on acceptance activities.

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. With regards to information

being provided to demonstrate compliance with applicable provisions of the Medical Device Quality System Regulation (21 CFR 820), this application was deficient. Additional information is required so that an appropriate review can be conducted. Also, more information will be needed from the applicant prior to making a decision about which facility or facilities would potentially need to be inspected.

Regulatory history evaluation

After reviewing the application, the (b) (4) site located at (b) (4), was identified as a facility subjected to applicable Medical Device Regulations under 21 CFR part 820.

An analysis of the firm's inspection history over the past 2 years showed that a device inspection conducted on (b) (4), revealed multiple deficiencies and was classified VAI. The inspection focused on the OEM liquid dispenser [syringe] product. The following QSIT subsystems were covered during the inspection: Management Controls, CAPA, Design Controls, P&PC, Document Controls and Purchasing Controls. A 5-item form FDA 483 was issued to the firm at the conclusion of the inspection. The observations included CAPA, complaints, calibration, and document control.

Determination whether an inspection of the manufacturing facilities is required will not be made at this time until the firm provides the additional information related to the finished combination product manufacturing activities.

Update:

The firm confirmed (b) (4) located at (b) (4), is the primary supplier and manufacturer of oral dispenser and press in bottle adapter. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. FACTS revealed that the firm is listed a "not a workload obligation". The firm is registered with FDA as a "Manufacturer". The firm is not responsible for manufacturing the final combination product; therefore, an inspection is not required for this firm.

Additionally, the firm noted that the drug product manufacturer and the final combination product manufacturer is DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701. An analysis of the firm's inspection history over the past 2 years revealed that a medical inspection at the facility has not been conducted. The most recent inspection was performed on (b) (4).

This inspection was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) No FDA-483, Inspectional Observations, was issued and the inspection was classified as NAI. The previous inspection of the firm was conducted on (b) (4). This was a drug preapproval inspection and covered NDA (b) (4) and ANDA (b) (4) This inspection covered the new facility, equipment, and process and associated controls including automation, analytical, environmental, microbiology, and formulation and testing of (b) (4). An FDA-483 was issued, and the inspection was classified VAI. The district recommended approval of ANDA (b) (4) ANDA (b) (4) An inspection was also conducted on (b) (4) and covered GMPs of sterile and non-sterile dosage forms, as well as Pre-Approval coverage for NDA (b) (4) (b) (4) filed to transfer manufacture and testing of the finished product to this site. This inspection is classified NAI and approval was recommended for NDA (b) (4) The firm is responsible for manufacturing the final combination product; therefore, an inspection is required for this firm. CDRH/OC recommends a post-market approval inspection of DPT Laboratories, Ltd. located at 1200 Paco Way Lakewood, New Jersey 08701.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of application NDA 205525 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product and it is requested that the below be communicated to the firm:

1. Because your product is a combination product, you are reminded that Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

   A review of your submission found that documentation to demonstrate compliance with applicable 21 CFR 820 regulations was not provided. In your response to this letter, please provide all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations (Management Controls, Design Controls, Purchasing Controls and Corrective and Preventive Actions).

Suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

Firm's response:

The applicant noted that the combination product is manufactured at DPT Laboratories, Ltd. Therefore, the firm provided DPT procedures.

Management Control (21 CFR 820.20):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control (21 CFR 820.30):

(b) (4)

(b) (4)



The information provided by the firm has adequately addressed the requirements of 21CFR 820.30.

Purchasing Controls (21 CFR 820.50):

(b) (4)



The information provided by the firm has inadequately addressed the requirements of 21CFR 820.50.

Deficiencies to be conveyed to the applicant:
Insys Therapeutics, Inc. is responsible for the final combination product. Your November 30, 2015 response noted (b) (4) **Please provide a description of your supplier evaluation process and a description of your purchasing controls.**

Corrective and Preventive Action (CAPA) (21 CFR 820.100):

(b) (4)

The information provided by the firm has adequately addressed the requirements of 21CFR 820.100.

2. In your response, please provide the name of the facility or facilities that perform the manufacture of the combination product and constituent parts including each facility's responsibility. Additionally, your response should include the facility that was responsible for developing the Dronabinol Oral Solution design specifications, and the facility that maintains the design history file for the finished combination product. Lastly, please provide the name of the facility or facilities that maintains the records for Design Controls; Corrective and Preventive Action; and Purchasing Controls.

Firm's response:

The applicant provided a table containing the name of the facilities that perform the manufacture of the commercial combination product and constituent parts, including each facility's responsibility.

Name of the facility	Responsibility
(b) (4)	Primary supplier of oral dispenser and press in bottle adapter
DPT Laboratories, Ltd. 1200 Paco Way Lakewood, NJ 08701	(b) (4) manufacturing, (b) (4) (b) (4) packaging and labeling, analytical release and alternate stability testing site – Syndros Oral Solution
(b) (4)	Primary supplier of clear amber (b) (4) glass 30 mL bottle
	Primary supplier of white polypropylene child - resistant cap lined with (b) (4) iner (b) (4) liner coated with a Teflon film)
	Primary supplier of (b) (4) cap liner (b) (4) liner coated with a Teflon film) (b) (4)

The firm noted DPT maintains records of design controls or specifications, CAPA and Purchasing controls with oversight from Insys Therapeutics. DPT and Insys Therapeutics have a Quality Agreement in place.

3. The information provided was insufficient to verify that the acceptance activities conducted on supplied device constitutes parts to ensure the safety and effectiveness of the finished combination product. Additionally, the descriptions of the manufacturing activities of the finished combination product were not provided. The application did not include information on how the finished combination product would be assembled.

Firm's response:

Acceptance criteria for incoming controls performed by DPT site for the device components were included in NDA Section 3.2.R.4.6.

Table 5: Oral Dispenser Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification
Graduations Accuracy	(b) (4)	Gravimetric

Table 6: Press-in bottle adapter Specifications and Analytical Procedures

Test	Acceptance Criteria	Analytical Procedure
General Appearance	Complies	Visual
Dimensions	Complies with Supplier Technical Drawing	Caliper Measurement
Material verification	Complies	Visual verification and supplier CoA verification

Device manufacturer ([redacted] (b) (4)) performs the release testing on the device components prior to shipment to DPT. During the development, Insys Therapeutics also performed device functionality testing to confirm the suitability, safety and effectiveness of the finished combination product and results were provided in NDA (refer to Sections 3.2.R.4.3 and 3.2.R.4.4).

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application Dronabinol Oral Solution and has the following recommendations:

Application Dronabinol Oral Solution approvability under the Medical Device Regulations should be delayed until the sponsor provides the additional information requested and an adequate desk review of the application has been completed.

Bleta Vuniqi -S

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Bleta Vuniqi

Prepared: BVuniqi: October 26, 2015
Reviewed: VVerna: October 28, 2015
Revised: BVuniqi: February 29, 2016
Reviewed: VVerna:March 1, 2016

CTS No.: ICC1500308

Response: CTS No.: ICC1600112

NDA 205525

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

/s/

MAUREEN D DEWEY
03/09/2016

M E M O R A N D U M

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

Date: February 26, 2016

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Silvia N. Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 205-525 for Dronabinol Oral Solution (Oral solution: 150 mg/30 mL, or 4.25 mg/0.85mL delivered dose)
Indication(s): For the treatment, in adults, of:
1) Anorexia associated with weight loss in patients with AIDS; and
2) Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.
Dosage:
Indication #1: (b) (4) mg BID, maximum daily dose
Indication #2 (b) (4) mg/m2 prior to chemotherapy, then every 2-4 hours up to 4-6 doses/day
Sponsor: Insys Therapeutics, Inc.

Materials Reviewed: Clinical Trial INS-13-017- A Single-Dose, Double Blind, Double-Dummy, Randomized, Placebo and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Dronabinol Oral Solution in Recreational Cannabinoid Users Study Report

In vitro study of Abuse Potential Comparison of Dronabinol Oral Solution with Marinol or its Generic Equivalent Dronabinol Capsules USP (Protocol CHP12009)

Response to Information Request dated December 30, 2015, Study Report, In vitro study of Abuse Potential Extraction Studies for Comparison of Dronabinol Oral Solution with Marinol or Dronabinol Capsules USP (Protocol CH0022), and Study Report, In vitro Study of Abuse Potential Smoking/Vaporizing Studies for Comparison of Dronabinol Oral Solution with Marinol or its Generic Equivalent Dronabinol Capsules USP (Protocol CH0023)

DARRTS, IND 75228 CSS Consult; Randall-Thompson, Jovita 4/12/2012
DARRTS, IND 75228 CSS Consult; Bonson, Katherine 11/16/2012

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Reference ID: 3893828

I. SUMMARY

1. Background

This memorandum responds to a consult request dated August 13, 2014, from the Division of Gastroenterology and Inborn Errors Products (DGIEP) to review the data submitted under NDA 205-525 to assess the abuse potential of Dronabinol Oral Solution, and recommend appropriate scheduling of the formulation under the Controlled Substances Act (CSA). Initially the application was refuse to file based on the lack of an adequate and complete pediatric study plan to conduct studies to assess the safety and effectiveness of the product for the treatment of nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric patients who failed to respond adequately to conventional antiemetic treatments. The application was resubmitted on June 1, 2015.

Dronabinol Oral Solution contains 5 mg of dronabinol per mL of a sweetened 50 %w/w alcoholic solution and is available in 30 mL bottles. The product's proposed indication is for the treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS), and for the treatment of CINV in patients who have failed to respond adequately to conventional antiemetic treatments.

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 (Gaoni and Mechoulam, 1964)), and is currently controlled in Schedule I of the CSA.

Synthetic dronabinol in Dronabinol Oral Solution is the same active pharmaceutical ingredient (API) in the FDA-approved product, Marinol capsules, which is currently a Schedule III product under the CSA. The therapeutic indications for which Dronabinol Oral Solution is proposed are identical to the FDA-approved therapeutic indications of Marinol capsules. However, Dronabinol Oral Solution is controlled under Schedule I of the Controlled Substances Act (CSA) given that its primary active drug, synthetic delta-9-THC, is listed as a Schedule I substance [21 CFR 1308.11(d) (30)] and that a solution of dronabinol does not meet the criteria specified under 21 CFR 1308.13 (g) (1) to be controlled under Schedule III of the CSA. Dronabinol Oral Solution is recommended for placement in a different Schedule, upon FDA approval. The Sponsor has requested to place their product under Schedule III of the CSA, based on the view that their product is similar to Marinol capsules.

FDA approved Marinol capsules for marketing on May 31, 1985. At the time of approval, Marinol was rescheduled from Schedule I to Schedule II based on its accepted medical use and high abuse potential (51FR 17476). On July 2, 1999, Marinol was rescheduled from Schedule II to Schedule III (64 FR 35928). In this second rescheduling action, DEA found that the formulation of the product in sesame oil, the difficulty in separating the active ingredient from the formulation (which limits its abuse by the oral route of administration), and its delayed onset of behavioral effects by the oral route supported a finding of a lower abuse potential relative to substances in Schedule II (Sapienza, 2006). The rescheduled product is described under 21 CFR 1308.13 (g) (1) as "Dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product." It is important to note that 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.

Reference ID: 3893828

The following sections provide conclusions and recommendations. A review of the materials submitted by the Sponsor to characterize the abuse potential of the formulation for labeling and scheduling purposes can be found under the Discussion section.

2. Conclusions

1. **The Product[1] is currently listed in Schedule I of the CSA. If approved for marketing, in order for the Product to be legally marketed, it must be rescheduled to a lower schedule of the CSA. The abuse liability properties of Marinol (Schedule III), the only other approved dronabinol-containing drug product, are used for comparison with the Product. Marinol is formulated (dissolved in sesame oil in a hard capsule) in a manner that vitiates the abuse liability of the API, dronabinol.**

2. **The Product is easily manipulated for abuse by inhalation and oral routes.** The in vitro study data demonstrate that the Dronabinol Oral Solution can be manipulated to afford highly concentrated dronabinol extracts that can be abused by the inhalation route. Additionally, 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 oral abuse. CSS has concluded that the Dronabinol Oral Solution has a greater potential for abuse than the Marinol capsules and presents a greater risk of unintentional overdose if abused.

3. **The formulation of the Product has important differences from Marinol that facilitate product manipulation.** Data from in vitro studies conducted by the Sponsor do not support their claim that the Dronabinol Oral Solution and Marinol capsules are chemically similar. Dronabinol Oral Solution is easier to handle than the Marinol capsules and can be easily concentrated by evaporation when exposed to minimal heat. In addition, a higher percentage of dronabinol is extracted in methylene chloride from the Dronabinol Oral Solution than from the Dronabinol capsules using the best solvent for extraction identified by the Sponsor. Thus, in vitro manipulation studies demonstrate that Dronabinol Oral Solution can be successfully manipulated to afford highly concentrated extracts in solvents that can be easily evaporated to give high content dronabinol residues that can be abused by smoking or through other routes of abuse.

4. **Product has inherent PK/PD properties that make it potentially more abuseable than Marinol.** Although Dronabinol Oral Solution and Marinol capsules can be abused by oral ingestion, the 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 abuse. Additionally, although not assessed by the Sponsor, the Dronabinol Oral Solution product 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.

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[1] Product refers to Dronabinol Oral Solution (NDA 205525)

Reference ID: 3893828

The ease of manipulation of the Oral Solution and the fact that it may serve as an easily accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) for purposes of abuse indicate that Dronabinol Oral Solution will be preferentially targeted for abuse over Marinol capsules. Thus, it is concluded that the Dronabinol Oral Solution has a higher potential for abuse than the Marinol capsules and presents a higher risk of unintentional overdose, especially if abused.

5. **Physical manipulation of the Product is easier than that of Marinol.** Removing the formulation of the Dronabinol Oral Solution from the dispenser or the sesame oil formulation from the capsules would be the first step in the manipulation of the formulation for purposes of abuse. In vitro studies demonstrated that it is easier and more efficient to remove the Dronabinol Oral Solution from the dispenser than to remove the sesame oil formulation from capsules. The Sponsor did not conduct specific studies to show this difference, however, a loss of approximately 30 % recovered API was reported in the preparation of the sesame oil sample for the drying studies. As part of the drying studies, the Sponsor took the content of one capsule of Marinol into a syringe, and measured the amount of API recovered from the sample. Although the sample was not subject to any further manipulation, a high percentage of the API was lost in the process. The loss of recovered API may be explained by the loss of the sesame oil formulation due to the adherence of the oil to any instrument used to handle the samples. (See Discussion section, Table 2).

6. **The API in the Product can more easily be extracted than from Marinol**. Extraction studies showed that a higher percentage of dronabinol is extracted in methylene chloride from the Dronabinol Oral Solution, than from the Dronabinol capsules using the best solvent for extraction identified by the Sponsor. Methylene chloride extracted on average over 85 % of the API from the Oral Solution, while on average 65 % of API was extracted from the Dronabinol capsules in ethanol.

   The Sponsor concluded that extraction of the API from the Dronabinol Oral Solution and Marinol or Dronabinol capsules USP is feasible. The Sponsor further concluded that the extraction of the API from the Dronabinol Oral Solution is not more efficient or that it would afford larger quantities of the API than the extraction from Marinol capsules, based on the assumption that a high volume of methylene chloride would have to be used to recover large quantities of dronabinol from the Oral Solution and that it will take longer to evaporate this solvent. However, the use of higher volumes of the solution and of extraction solvents does not impede the ability to extract larger amounts of dronabinol from the oral solution. In some instances, the use of larger volumes may actually increase the efficiency of the extraction by decreasing the losses that result from working with small samples.

7. **The Product can easily be abused by inhalation (smoking and vaping).** In vitro evaporation studies (drying studies) showed that the alcohol component of the Dronabinol Oral Solution is readily volatilized when exposed to minimal heat, affording concentrates that can be used for smoking or vaping or, as the Sponsor claims, to be used intranasally. However, the Sponsor did not conduct smoking or vaping studies with these concentrated residues. The Sponsor limited the use of these concentrates to the application of the residues to tobacco paper, and did not use these concentrates to spike traditional tobacco cigarettes or in vaporization studies using e-

cigarettes. Though the Sponsor conducted these studies to explore the feasibility of abusing these concentrates through the intranasal mucosa, the intranasal route does not seem to be a common route of abuse of dronabinol.

From the sources of heat tested, the heat lamp and microwave oven seemed to have worked better than the hot plate and water bath. These heat sources gave smaller residues, good API recovery, and lower levels of impurities. On average, the amount of API recovered ranged from 9.3 mg to 9.75 mg out of 10 mg, depending on the evaporation method used, and on average the Dronabinol Oral solution lost approximately 84 % of its initial weight using a heat lamp after drying for 1.5 hours and on average 87 % of its initial weight using a microwave for 1 minute.

8. **Sponsor's smoking studies showing Product similarity to Marinol capsules has major deficiencies.** As smoking is the most common route of abuse of dronabinol containing products, the Sponsor evaluated the feasibility of smoking traditional cigarettes spiked with the Dronabinol Oral Solution or with the content of Marinol capsules. In the hands of the Sponsor, it was not possible to smoke the Dronabinol Oral Solution or the Marinol capsules. However, many deficiencies were noted regarding the way these studies were conducted (See Discussion section, Subsection 1.2.3 Smoking Studies for a complete list of deficiencies).

   a. The Sponsor conducted studies to evaluate the amount of dronabinol that could be inhaled by vaporization of the Dronabinol Oral Solution or of the contents of Marinol capsules using the Volcano vaporizer. Under the experimental conditions set by the Sponsor the amount of vaporized dronabinol (THC) using the Volcano apparatus was low. The addition of propylene glycol to the formulations increased the amount of dronabinol vaporized from the Dronabinol Oral Solution; however, recovered dronabinol levels remained low.

   b. The Sponsor concluded that the Volcano is not efficient in vaporizing dronabinol from the Dronabinol Oral Solution or from the Dronabinol capsules. It seems that the experimental conditions chosen by the Sponsor may not have been the best ones to optimize greater levels of dronabinol vaporization. The studies conducted by Solowij et al., 2014, using the Volcano vaporizer and THC samples applied to the Volcano Liquid Pad in ethanol demonstrate that up to 78 % of THC could be recovered at the same temperature of vaporization used by the Sponsor. The discrepancy between the data collected by the Sponsor and published data may be due to the manner in which samples were prepared and applied to vaporization pad, as well as the way the vapors were collected. Study results more aligned with published data could have been achieved if formulation extracts taken in ethanol were loaded into the Volcano Liquid Pad, instead of the loading of the formulations without prior manipulation.

   c. The Sponsor conducted studies to assess the feasibility of vaping the Dronabinol Oral Solution and the contents of Marinol capsules using a specific type of electronic cigarette. These studies showed a low recovery of dronabinol from vaporization of the non – manipulated samples of the formulations or from extracts in ethanol under the experimental conditions chosen. However, these studies are not conclusive because no validation of the conditions chosen including the type of e-cigarette selected, the temperature and power of the vaporizer, the solvent selected in the preparation of the samples, the smoking procedure

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selected, and the smoking machine used was not provided or conducted. (See Discussion section, Subsection 1.3.3 Smoking Studies for a complete list of deficiencies).

9. **As a sweet alcoholic solution of dronabinol, the Product is formulated to be appealing to users and abusers.** 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.

10. **The Product mediates a greater array of psychiatric AEs.** The Dronabinol Oral solution label indicates that the occurrence of psychiatric symptoms increases significantly at the maximum dose of 12 (b) (4) mg/m2. The Marinol label, (b) (4) indicates that in antiemetic studies following oral doses of 0.4 mg/kg (28 mg/70 kg) significant CNS symptoms such as amnesia, confusion, delusions, depression and hallucinations were observed. In the human abuse potential study (Clinical Trial INS-13-017) there were more psychiatric AEs (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.

11. **The risk of overdose with dronabinol products is described** (b) (4) . Signs and symptoms of overdose include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth, tachycardia, memory impairment, depersonalization, mood alteration, urinary retention, reduced bowel motility, decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

12. **The human abuse potential (Clinical Trial INS-13-017) study confirmed that Dronabinol Oral Solution has an abuse potential comparable to that of Marinol in recreational cannabis users *when taken as prescribed, following administration of single doses no greater than 30 mg.*** This study demonstrated that the abuse potential of Dronabinol Oral Solution (10 mg and 30 mg) is essentially the same as the positive control Marinol (10 mg and 30 mg), based on the pre-defined primary and key secondary endpoints: peak effects of Drug Liking (at the moment) and High VAS, areas under VAS curves during the treatment period, Overall Drug Liking measured using VAS (at 12-h and 24-h post-dose in treatment phase), and Take Drug Again measured using VAS (at 12-h and 24-h post-dose in treatment phase). The differences between Marinol at either high or low dose and Dronabinol at either high or low dose are not statistically significant in the primary and key secondary PD endpoints. At the highest doses of Marinol tested (30 mg) the mean Drug Liking VAS (Bipolar scale, where 50 represent neither like or dislike, 0 scores represent strong disliking and 100 strong liking) mean scores were 89.0 (SD: 13.30) for Marinol 30 mg capsules and 91.7 (SD: 11.51) for Dronabinol Oral Solution.

Dronabinol and Marinol demonstrated statistically significant abuse-related subjective effects compared to placebo. There were no statistically significant differences between comparable single doses of Marinol and Dronabinol on any of the primary or key secondary endpoints. Multiple dosing effects and drug liking at higher doses were not evaluated.

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

13. **As stated in the Marinol label and in the Dronabinol Oral Solution label, CNS adverse reactions are dose-related, increasing in frequency with higher doses, and subject to inter-patient variability.** The Dronabinol Oral solution label further indicates that the occurrence of psychiatric symptoms increases significantly at the maximum dose of 12 (b) (4) mg/m^2. The Marinol label, (b) (4) indicates that in antiemetic studies following oral doses of 0.4 mg/kg (28 mg/70 kg) significant CNS symptoms such as amnesia, confusion, delusions, depression and hallucinations were observed.

14. **In the State of Colorado, where there is a wide variety of products infused with delta-9-THC, policymakers have considered imposing caps on all recreational edibles at 10 mg delta-9-THC (one tenth of the currently allowed levels) (National Conference of State Legislatures, 2015).** 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 abuse. This further illustrates the potential risk to the public health associated with the recreational ingestion of the large amounts of delta-9-THC found in Dronabinol Oral Solution.

15. **Based upon the results from the in vitro studies discussed in this review, the large quantity of dronabinol in the supplied Product, its pharmacokinetics when taken orally, and principle contribution to marijuana psychoactivity (Schedule I), the abuse potential of the Dronabinol Oral Solution is higher than the abuse potential of drugs in Schedule III.**

II. Recommendations

1- Although the human abuse potential study conducted by Sponsor demonstrates that the Dronabinol Oral Solution has an abuse potential comparable to that of Marinol in recreational cannabis users when taken in single doses (no greater than 30 mg), as prescribed, the in vitro study data demonstrate that the formulations differ in their physicochemical properties, which affects how and the extent to which the drug can be abused. The Dronabinol Oral Solution can be manipulated to afford highly concentrated dronabinol extracts that can be reconstituted for smoking using vaporizers such as electronic cigarettes (e-cigs) or the Volcano vaporizer. Although the intravenous abuse of dronabinol is not a common route of abuse, the concentrated

extracts of dronabinol in solvents that can be easily evaporated afford residues that could be reconstituted for intravenous abuse.

When considering the oral route of abuse, Dronabinol Oral Solution serves as an accessible source of a large amount of dronabinol (150 mg of dronabinol in 30 mL of a 50% w/w alcoholic solution) that can be easily abused orally.

2- Dronabinol Oral Solution has a greater potential for abuse than Marinol capsules and presents a higher risk of unintentional overdose, if abused. Accordingly, a recommendation to place Dronabinol Oral Solution in Schedule II of the Controlled Substance Act will follow.

3- Regarding labeling of Dronabinol Oral Solution, CSS recommends the inclusion of a warning indicating that high drug content in the dispensed product adds to the risk of adverse outcomes from abuse and misuse of the formulation.

III. Discussion

1. Chemistry

1.1. Product description and product composition

The product consists of a solution of dronabinol for oral consumption. Dronabinol, the active ingredient, is of synthetic origin. It is a light-yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in an alcohol/water mixture. It has a pKa of 10.6 and an octanol-water partition coefficient 6,000:1 at pH7. These measurements indicate that half of the dronabinol will be ionized at a pH of 10.6 or higher, and the solubility of dronabinol will be higher in non- polar solvents depending on the pH and temperature.

As shown in **Table 1**, the product contains 5 mg of dronabinol /mL of a 50% W/W alcoholic solution. Other ingredients include sucralose, antioxidants, preservatives and co-solvents. Thirty mL of the product will be supplied in clear, amber-glass bottles. Thus, each product bottle will contain 150 mg of dronabinol. Based on pharmacokinetic studies, these 150 mg of dronabinol in solution are equivalent to 176 mg of dronabinol in sesame oil capsules. Dronabinol Capsules USP are available in 2.5 mg, 5 mg and 10 mg strengths in bottles containing 60 capsules per bottle.

Table 1: Product Composition (Data reproduced from NDA 205,525)

Component	Quality Standard	Function	Concentration % w/w
Dronabinol	USP	Active Ingredient	0.541 (5mg/mL)
Butylated Hydroxy Anisole (BHA)	USP	Antioxidant	0.01
Sucralose	USP?NF	Sweetener	0.05
Methyl Paraben	USP/NF	Preservative	0.02
Propyl Paraben	USP/NF	Preservative	0.02
PEG 400	USP/NF	Co-solvent	12.0
Propylene Glycol	USP	Co-solvent	5.50
Water	USP	Solvent/Diluent	31.859
Dehydrated Alcohol (Content 50.0 %w/w)	USP	Co-solvent	QS

1.2. In vitro Manipulation Studies

In vitro manipulation studies were designed and conducted by the Sponsor to evaluate the abuse resistant properties of the formulation. Marinol or Dronabinol USP 10 mg capsules (Synthetic Delta-9-THC in sesame oil) was chosen as the positive comparator in these studies. Dronabinol capsules are controlled in Schedule III of the Controlled Substances Act (CSA) based on epidemiological data and on predicted difficulty to smoke the sesame oil formulation. The most common routes of abuse of THC containing products are smoking and oral ingestion. The Sponsor also evaluated the ease with which the Oral Solution and Marinol could be concentrated to be available for intranasal abuse. Additionally, the Sponsor evaluated the feasibility of preparing samples for injection.

The Sponsor used existing validated HPLC analytical methods developed (CH.19) for qualitative purposes.

The Sponsor conducted studies to investigate abuse potential by assessing the manipulation of the solution for intravenous, intranasal or inhalation (smoking) routes. Insys conducted the following studies:

1. Manipulation of the formulations for syringeability or injectability
2. Drying of the formulation at room temperature, and with heat (hair dryer, oven, microwave oven), to give a concentrate of dronabinol
3. Smoking studies

The following sections provide an overview of the studies and a summary of the findings under each condition.

1.2.1. Manipulation of the formulations to remove the content for the purpose of preparing a solution for injection.

For Dronabinol Oral solution 5 mg/mL
For injectability studies, the Sponsor recorded the ease of withdrawing 2 mL of the oral solution into a syringe, and the ease of expelling the solution through a 25 gauge needle, as well as quantification of the amount of drug taken into the syringe.

For Marinol
For injectability studies using Marinol, the Sponsor collected the content of several capsules into a vial to obtain 2 mL of the sesame oil product, and to facilitate syringeability of the product, the sample was diluted with 2 mL of alcohol. Due to the difficulty of withdrawing the sesame oil product using a 25 gauge syringe, the Sponsor had to use an 18 gauge needle instead to conduct these studies.

The Sponsor did not describe how the capsules were manipulated (cut, or treated with solvents to break the outer shell) in order to withdraw the 2 mL of the sesame oil formulation

Conclusions: The capsules contents were harder to take into a syringe, and difficult to expel, probably due to pieces of capsule shell blocking the needles requiring high bore needles (18 gauge). These studies demonstrated that handling and administration of the oral solution is easier than the capsules. For the specific purpose of these studies, it could be concluded that it will be easier to inject Dronabinol Oral Solution than the contents of the Marinol capsule, although the intravenous abuse of THC containing products is not a common route of abuse.

1.2.2. Drying of the formulation at room temperature, and with heat (hair dryer, oven, microwave oven), to give a concentrate of dronabinol

The Sponsor conducted in vitro studies to concentrate the formulation by evaporation of the solution with heat (hot plate, microwave oven, maintaining the sample in a water bath, and by a heat lamp). These studies are referred in this section as drying studies

Drying studies were performed on 2 mL (10 mg of dronabinol) of Dronabinol Oral Solution and on the amount of product withdrawn from one capsule of Marinol under several conditions. The samples obtained were evaluated gravimetrically and for overall recovery and purity of the API. Studies were performed by duplicate under the following drying conditions and using the following devices. Findings are summarized below and shown in **Table 2**.

- Hot plate (110 °C) for 45 minutes- The oral solution sample was reduced and turned yellowish. Oily residue remained. Residue quickly went into ethanol (97.5 % API recovery, 2.58% average impurity, and average weight of residue 345.64 mg). Information provided by the Sponsor on January 29, 2016, in response to a discipline request indicates that there was approximately an average loss upon drying of 81 % of the initial weight of the sample, with an average initial weight of samples of 1836.59 mg.
- Heat lamp (250W) for 1.5 hour- Solution turned yellow and small brown specks were observed in solution. Specks were dissolved in ethanol, though not completely (96% API recovery, 3.51% average impurity, and average weigh of residue 290.62 mg). Information provided by the Sponsor on January 29, 2016, in response to a discipline request indicates that there was approximately an average loss upon drying of 84% of the initial weight of the sample, with an average initial weight of samples of 1837.44mg.

- Microwave Oven (700W), 1 minute intervals for 7 minutes- a 2 minute oral solution turned yellowish, at 3 minutes small brown specks were observed floating. At 4 minutes, vapor was observed and the solution turned darker yellow, no further changes at 5-7 minutes. Residue was dissolved in ethanol, though brown small particles were observed. (92.7 % API recovery, 3.19 % average impurity, and average weight of residue 237.79 mg). Information provided by the Sponsor on January 29, 2016, in response to a discipline request indicates that there was approximately an average loss upon drying of 87% of the initial weight of the sample, with an average initial weight of samples of 1839.3 mg.
- Water Bath at 85 °C for 1 hour. Solution was cloudy and small brown swirls were observed in solution. The swirls turned into droplets first when dissolved in ethanol. (97.3 % API recovery, 2.40 % impurity, and average weight of residue of 558.98 mg). Information provided by the Sponsor on January 29, 2016, in response to a discipline request indicates that there was approximately an average loss upon drying of 69.5%% of the initial weight of the sample, with an average initial weight of samples of 1834.71mg).
- No evaporation of the content of a Marinol capsule was attempted. The content of 1 capsule was taken into a syringe with a 71.1% API recovery. The content of the Marinol capsule was withdrawn into a syringe.

Conclusions: In vitro evaporation studies (drying studies) showed that the alcoholic component of the Dronabinol Oral Solution is readily volatilized when exposed to minimal heat, affording concentrates that could be used for smoking or vaping or, as the Sponsor claims, to be used intranasally. However, the Sponsor did not conduct smoking studies using these concentrated residues, and the intranasal route seems not to be a common route of abuse of dronabinol

These studies also showed that the heat lamp and microwave oven seemed to have worked better than the hot plate and water bath. These heat sources gave smaller residues, good API recovery and lower levels of impurities. On average, the amount of API recovered ranged from 9.3 mg to 9.75 mg out of 10mg, depending on the method of evaporation used, and on average the Dronabinol Oral Solution lost approximately 84 % of its initial weight using a heat lamp after drying for 1.5 hours and on average 87 % of its initial weight using a microwave for 1 minute.

Table 2: In vitro drying studies conducted with Dronabinol Oral Solution

Drying Studies		**Dronabinol Oral Solution 2 mL (10 mg Dronabinol, THC)**			
Conditions	Average weights (mg)	Average THC % Recovery	Average THC % Impurity	THC Concentration % weight (mg)	Observation
Hot Plate 110 °C 45 minutes	Initial: 1,836.59 Final: 345.63 % Loss: 81	97.5	2.58	Initial: 0.54 Final: 2.82	• Sample turned yellowish • Oily residue remained • Residue went quickly into ethanol
Heat Lamp 250 W 90 minutes	Initial: 1,837.44 Final: 290.62 % Loss: 84	96.0	3.51	Initial: 0.54 Final: 3.3	• Sample turned yellow • Brown specs observed in solution • Specs went into ethanol
Microwave Oven 700 W 1 minute intervals for 7 minutes	Initial: 1839.30 Final: 237.79 % Loss: 87	92.7	3.19	Initial: 0.54 Final: 3.89	• Sample turned yellowish • Brown specs observed floating • Residue went into ethanol. Small brown particles observed
Water Bath 85 °C 60 minutes	Initial: 1,834.71 Final: 558.98 % Loss &0	97.3	2.40	Initial: 0.54 Final: 1.74	• Sample cloudy • Brown swirls observed in solution • Swirls turned into droplets in ethanol
No Drying studies conducted with Dronabinol Capsules		**The content of a 10 mg capsule was taken into a syringe, 71.1 % THC recovered**			

1.2.3. Smoking studies

A common method of abusing THC is through smoking. Testing included direct application of Marinol and of an Oral Solution concentrate to tobacco rolling paper or to a cigarette. The feasibility of smoking the formulations using electronic cigarettes was not evaluated in the original application. However, the Sponsor evaluated the feasibility of using e-cigarettes and vaporizers such as the Volcano to deliver THC in response to a CSS Information Request, dated December 30 2015 (Response received on January 29, 2016).

- *Direct application of the formulations to rolling paper*.

The residue from evaporation of 2 mL of solution using the various methods described above (hot plate, microwave, and water bath and heat lamp) was added to tobacco rolling paper. Smoke and vapors were collected using a solvent trap upon burning of the papers, and the ease of burning the paper spiked with the drug residue was recorded. When the formulation was applied directly to the paper, the amount of product absorbed, appearance of the paper and the time required to dry the paper was recorded.

As expected, all attempts to use the rolling sheets spiked with the various concentrates for smoking purposes were unsuccessful, because papers turned into ash upon ignition rendering the samples not amenable to smoke The papers spiked with the sesame oil content of the Marinol capsules caught fire prior to complete burning.

- *Direct application of the formulations to one traditional tobacco cigarette*.

The content of six Marinol 10 mg capsules or 0.8 mL of the Dronabinol Oral Solution was absorbed into 1 cigarette. Samples were allowed to dry in a fume hood for 1.5 to 2 hours. The vapors were collected in a solvent trap with 10 mL of ethanol.

The cigarettes spiked with the Oral Solution burned in less than 15 minutes, whereas the ones spiked with the Marinol solution took approximately 27 minutes or less. The cigarettes spiked with the Oral Solution were less difficult to light than the ones spiked with Marinol. Once the vapors were collected, the ethanolic solution in the trap turned yellowish. The amount recovered from the moking/vaporization of the cigarettes spiked with Marinol was on average 0.105 mg (0.18 % of label claim), whereas the amount recovered using the Oral Solution was 0.02 mg on average (0.51% of label claim)

Conclusions: Attempts to burn cigarette papers saturated with evaporates of the Oral Solution or with the Oral Solution directly, or capsules contents were not successful because the papers burned too quickly and did not produce any vapors. Smoking cigarettes spiked with the Oral Solution or with the content of the dronabinol capsules were not successful either.

Deficiencies: The smoking studies as conducted by the Sponsor were not designed properly. The addition of a formulation sample directly to rolling paper did not change the expected outcome of the experiment. The rolling paper, as expected, turned into ashes with or without addition of the formulation when lighted.

Regarding the studies where both formulations were added to the cigarettes the following deficiencies are noted:

1- No description of the smoking apparatus was found in the report if any was used, and no description of the smoking procedure used was reported. For example, was a vacuum applied to lit cigarettes, and in intervals to draw smoke into the smoking apparatus to simulate the puffing or inhaling or to mimic smoking conditions?
2- Limited drying times of approximately 90 minutes were used when spiking regular cigarettes with both formulations. Longer drying times up to 24 hours may change the way the cigarettes burned and smoked.

3- Very limited descriptions were provided as to how the formulations were added to the cigarettes. For example, no information could be found to determine if the formulations were applied to the open end of a cigarette held in upright position, or applied to the side of the cigarettes.
4- The Sponsor did not include a regular untreated cigarette as a standard for comparison in the studies. The inclusion of such a standard would have also served the purpose of identifying the right smoking procedure or smoking conditions.
5- The Sponsor did not evaluate the potential of applying concentrated samples or extracts of the Dronabinol Oral Solution to traditional tobacco cigarettes.
6- The smoking studies conducted by the Sponsor were initially limited to the application of the Dronabinol Oral solution and of Marinol to regular tobacco cigarettes. In response to an information request dated December 30, 2015, the Sponsor conducted studies to assess the feasibility of vaping the oral solution and the contents of the Marinol capsules, as well as the reconstituted product extracts using representative electronic cigarette devices (E-cigs) and the Vaporizers such as the Volcano, which could be adapted for the vaporization of liquid samples or used for vaporizing cannabinoids from botanical samples.

1.3. Additional in vitro studies conducted by the Sponsor in response to FDA information request, dated December 30, 2015.

Upon review of the initial in vitro data provided by the Sponsor, on December 30, 2015, the FDA requested the following information:

1- Sponsor should provide the weight of the initial samples subjected to evaporation using various heat sources. When reporting study results from studies attempting to concentrate the dronabinol product using several heat sources, Sponsor has reported the weight of the residue obtained after evaporation of volatiles, and the amount and purity of the dronabinol recovered. However, Sponsor has not provided weights for the samples before applying heat. In the absence of these data, it is not possible to quantify concentration levels.

2- Sponsor should conduct extraction studies using non-water miscible solvents (e.g., methylene chloride, ethyl acetate) in which dronabinol is soluble to determine the ease with which dronabinol can be isolated from the product, and concentrated by evaporation of the solvents for inhalation use. If dronabinol were to be more readily extracted from the oral solution than from the capsules, the product may be more likely to be targeted for abuse.

3- Sponsor should conduct studies to assess the feasibility of vaping the oral solution and the contents of the
Marinol capsules, as well as the reconstituted product extracts using representative electronic cigarette devices (E-cigs), as well as using other vaporizers such as the Volcano. Electronic cigarettes are currently gaining popularity as a means of delivering THC concentrates. (Giraud, C., de Cesare, M, Berthet, A., Varlet V., Concha-Lozano, N., Favrat, B. 2015. E-Cigarettes: A Review of New Trends in Cannabis Use Int. J. Environ. Res. Public Health, 12, 9988-10008.)

On January 29, 2016, the Sponsor responded to the FDA information request. In addition to providing the initial sample weights for samples used in the drying studies, the Sponsor provided reports on

extraction studies (Report. CH.0022), and reports on smoking and vaporizing studies (Report. CH.0023). Reviews and findings of these reports are provided in the following section.

1.3.1. Extraction studies

At FDA's request, the Sponsor conducted studies to compare the potential for extracting the API from Dronabinol Oral Solution and Marinol capsules or Dronabinol capsules USP. In these studies, the Sponsor used the following non aqueous solvents to extract the API from the Dronabinol Oral Solution: Methylene chloride, ethyl acetate, hexane and toluene. To extract the API from the sesame oil capsules, the Sponsor used non-oil miscible solvents such as ethanol, methanol and acetonitrile.

These studies were conducted to measure the amount of API extracted from 2 mL (10 mg) of the Dronabinol Oral Solution and 660 mg of the sesame oil capsule formulation containing an equivalent amount of 10 mg of dronabinol sampled from the content of 50 capsules of Dronabinol 2.5 mg capsules.

When working with the Oral Solution, 2 mL of solvent were added to 2mL of the Oral Solution, samples were mixed in a vortex for 60 seconds, and the solvent layers allowed to separate for 45 minutes. Upon separation of organic layer, the samples were dried (supposedly at room temperature) under nitrogen. Studies were conducted in duplicate. Methylene chloride samples were allowed to dry for 50 minutes, hexane samples for 15 minutes and toluene samples for 35 minutes. Upon evaporation of the extraction solvents, the residues were dissolved in ethanol and the amount of API measured by HPLC. When using ethyl acetate, the Sponsor reported that the ethyl acetate did not separate from the Dronabinol Oral Solution. A clear colorless viscous residue was obtained upon evaporation of the methylene chloride, hexane and toluene layers. When using methylene chloride and toluene as extracting solvents over 85% of the API was recovered, whereas a 64 % of the API was recovered using hexane.

When working with Dronabinol capsules, 2 mL of the selected solvents (ethanol, methanol and acetonitrile) were added to 660 mg of the sesame oil formulation (10 mg of dronabinol). The samples were manipulated in a similar manner to the Dronabinol Oral Solution samples. Samples were vortexed for 60 seconds, allowed to separate for 30 minutes and dried for 75 minutes. Extraction with the three solvents tested afforded clear pale yellow viscous residues, and the levels of API extracted ranged from 43.6 % with acetonitrile, 54.2 % when using methanol and 65.5 % when using ethanol.

Conclusions: A higher percentage of the API is extracted in methylene chloride from the Dronabinol Oral Solution, than from the Dronabinol capsules using the best solvent for extraction identified by the Sponsor. Methylene chloride extracted on average over 85 % of the API from the Oral Solution, while on average 65 % of API was extracted from the Dronabinol capsules in ethanol.

The Sponsor concluded that extractability of Dronabinol from the Dronabinol Oral Solution and Marinol or Dronabinol capsules USP is comparable, based on the assumption that a high volume of methylene chloride would have to be used to recover large quantities of dronabinol from the oral solution and that it will take longer to evaporate this solvent. However, the use of higher volumes of the solution and of extraction solvents may not be seen as an impediment for extracting larger amounts of dronabinol from the oral solution, and in some instances, the use of larger volumes may increase the efficiency of the extraction by decreasing the losses that may result by measuring small samples. In addition, the studies conducted by the Sponsor demonstrate that handling the sesame oil formulation is more difficult than

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handling the oral solution, and that it may be expected that some of the oily formulation may be lost due to adherence to syringe or any other instrument used to take the sample from the capsules.

1.3.2. Vaporization studies using the Volcano vaporizer

At FDA's request, the Sponsor conducted in vitro studies using the Volcano vaporizer to determine the amount of THC that may be vaporized from Dronabinol Oral Solution and from Marinol for recreational purposes.

The Volcano is a table vaporizer designed and manufactured by Storz & Bickel from Tittlingen, Germany, to vaporize the volatile compounds from herbal materials. This vaporizer heats cannabis at a temperature where cannabinoids are vaporized (around 200 °C) but below combustion temperature. Though originally designed to vaporize botanical products, more recently an adaptor was designed allowing for the vaporization of liquids and oils. This adaptor known as Liquid Pad consists of a stainless steel wire that functions like the plant fibers of herbs. A protocol for the optimal delivery of THC, cannabidiol and mixtures of cannabidiol and THC was published by Solowij et al., 2014.

The Sponsor measured the amounts of THC vaporized from the Dronabinol Oral Solution and Dronabinol capsules by direct application to the Volcano solution holder (Liquid Pad) of 1 mL of the Oral Solution containing 5 mg of dronabinol, and by direct application of 660 mg of the sesame oil capsule formulation containing 10 mg of dronabinol to the solution holder. A second set of experiments were performed in the presence of propylene glycol by adding 1 mL of propylene glycol to 1 mL of the Oral Solution and adding equal amounts in weight of the propylene glycol to the 660 mg of the sesame oil capsules sample. The 660 mg samples of Dronabinol Capsules were withdrawn from the contents of several Dronabinol Capsules 2.5 mg (between 10 to 12 capsules). Samples were heated at 230 °C (446 °F) for 25 minutes. The vapors were collected using a solvent trap containing ethanol and analyzed for THC by HPLC. Under the conditions of the study, the Sponsor reported that when vaporizing Dronabinol Oral Solution, vapors become visible at 6 minutes and a faint white vapor continued slowly for 23 minutes, with low recovery of THC (average 0.198 mg, 4.0% of initial sample). No THC was recovered when using Dronabinol Capsules.

The Sponsor conducted similar studies to evaluate if the addition of propylene glycol to the samples had an effect on the amount of THC recovered. The addition of propylene glycol slightly improved the levels of THC recovered, and vaping times decreased. Approximately 0.390 mg of dronabinol was recovered from the Oral Solution, representing a 7.8 % recovery from the initial sample vaporized. Approximately 0.9 % of THC was recovered from the Dronabinol Capsules.

Conclusions: Under the experimental conditions set by the Sponsor the amount of vaporized THC using the Volcano apparatus was low. The addition of propylene glycol to the formulations increased the amount of THC vaporized from the Dronabinol Oral Solution; however recovered THC levels remained low.

The Sponsor concluded that the Volcano is not efficient in vaporizing dronabinol from the Dronabinol Oral Solution or from the Dronabinol capsules. As such, it appears that the experimental conditions chosen by the Sponsor were not the best ones to achieve greater levels of dronabinol vaporization. The studies conducted by Solowij et al., 2014 using the Volcano vaporizer and THC samples applied to the

Volcano Liquid Pad in ethanol demonstrate that up to 78 % of THC could be recovered at the same temperature of vaporization used by the Sponsor. The discrepancy between the data collected by the Sponsor and published data may be due to the way samples were prepared and applied to the vaporization pad, as well as the way the vapors were collected. Study results more aligned with the published data could have been achieved if formulation extracts taken in ethanol were loaded into the Volcano Liquid Pad, instead of the loading of the formulations without prior manipulation.

1.3.3. Vaporization studies using e-cigarettes

E-cigarettes give cannabis users the option of "vaping" cannabis or its extracts without being identified by the characteristic smell of cannabis smoke. In addition, it is claimed that e-cig aerosol possibly contains fewer harmful chemicals than ordinary marijuana joints. Second and third generation e-cigs are recognized as the best suited to vaping cannabis or its extracts These cigarettes operate by vaporizing a liquid known as e-liquid that typically contains nicotine, or have been adapted so as to be able to vape dry herbs, oil concentrates, or cannabis-based e-liquids (Giroud et al, 2015).

As described by Giroud et al., 2015, there are two common types of e-cigarettes. The first type known as "cartomizer," contains a heating coil (atomizer) and a synthetic filler material wrapped around the heating coil. The second type is known as "clearomizer," which includes a clear tank of a larger volume than the cartomizer and no filler material. Instead the clearomizer contains a disposable head that contains the coil or coils and wicks. The wicks absorb the liquid and feed it to the heating coil. Clearomizers seem to be the preferred type of e-cigs to vape cannabis. Some clearomizers can be disassembled to remove and replace the atomizer and coil or coils. Clearomizers and cartomizers are screwed onto a re-chargeable battery that supplies power to heat the coils and vaporize the e-liquid contained in the tanks. E-liquids enriched in cannabinoid can be used in e-cigs as a source of THC. THC concentrates are mixed and diluted with pure propylene glycol or with mixtures of polyethylene glycols and propylene glycol.

The Sponsor conducted studies to assess the feasibility of vaping the Dronabinol Oral Solution and the contents of the Dronabinol capsules using a Vaporesso 75VTC e-cig. The Sponsor measured the amounts of THC vaporized from the Dronabinol Oral Solution and Dronabinol Capsules by adding 1 mL of the Dronabinol Oral Solution containing 5 mg of dronabinol, and by direct application of 660 mg of the sesame oil capsule formulation containing either 10 mg of dronabinol or 40 mg of dronabinol to the e-cig tank. A second set of experiments was performed in the presence of propylene glycol by adding 1 mL of propylene glycol to 1 mL of the oral solution and adding equal amount in weight of the propylene glycol to the 660 mg of the sesame oil capsules samples. The 660 mg samples of Dronabinol Capsules containing an equivalent amount of 10 mg or 40 mg of dronabinol were withdrawn from several 2.5 mg or 10 mg Dronabinol capsules (between 10 to 12 capsules).

Study results show that the amount of recovered dronabinol from the solution or from the capsules is low, and the addition of propylene glycol increases the recovery of dronabinol, though the recovery remains low. The Sponsor reports a 4% recovery of the initial 5mg contained in 1 mL of Dronabinol Oral solution, 6.2 % from the initial 10 mg contained in 660 mg of sesame oil formulation withdrawn from several 2.5 mg Dronabinol Capsules, and 7.1 % from the initial 40 mg contained in 660 mg of sesame oil formulation withdrawn from several 2.5 mg Dronabinol Capsules in the presence of propylene glycol.

Lower recovery of dronabinol was reported from vaporization of the extract residues reconstituted in ethanol. Methylene chloride was used as the extraction solvent when using the Oral Solution and ethanol was used to extract dronabinol from Capsules.

Conclusions: A low recovery of dronabinol from vaporization of the non –manipulated samples of the formulations or from extracts in ethanol under the experimental conditions chosen was observed. However, these studies are not conclusive because the experimental conditions chosen by the Sponsor are questionable, as pointed out in the Deficiencies section that follows.
Deficiencies:
After review of these studies, and considering that the amounts of THC in the vapor produced by e-cigs, is probably highly variable and depends on the vaporization technology, the temperature and power of the vaporizer, the type of cannabis product, and the puffing behavior (Etter, 2015), the following deficiencies are noted:

1- No justification for the selection of the cartomizer e-cig was provided.
2- A detailed protocol of the smoking procedure used and the type of smoking apparatus used to draw vapor into the ethanol trap was not provided.
3- No justification for selection of the smoking volume was provided.
4- The Sponsor chose the wrong vaporization solvent when vaporizing the reconstituted formulation extracts using e-cigs. The Sponsor chose ethanol to prepare samples for vaporization when using extracts of both formulations, when E-liquids containing propylene glycol and polyethylene glycol are the preferred solvents for use in e-cigs.
   Interestingly enough, for the Volcano vaporizer the Sponsor used propylene glycol to reconstitute the extract samples, when ethanol is the recommended solvent for that purpose when using the Volcano.
5- No standard or positive control sample was included in these studies to validate the experimental conditions selected.

2. Clinical Studies

2.1. Human Abuse Potential Study

Human Abuse Potential Study Background

Dronabinol, the (-) isomer of Δ9-tetrahydrocannabinol (THC), is a Schedule I substance. The first dronabinol-containing formulation approved by the FDA (as a Schedule II), was Marinol in 1985. In 1998, the Drug Enforcement Administration (DEA) rescheduled the formulation into Schedule III following review of post-market research on its abuse liability.

Dronabinol is synonymous and identical in chemical structure to delta-9-tetrahydrocannabinol and, with the exception of the Marinol formulation, THC compounds are Schedule I substances, covered under 21 CFR 1308.11(d) (31) definition of "tetrahydrocannabinols." Dronabinol is not listed in Schedule III under the CSA. Schedule III drugs (listed in 21 CFR 1308.13, paragraph (g) specifically identifies the Marinol formulation, as follows: (g) *Hallucinogenic substances.* (1) Dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product--7369.

In April 2012, during the IND stage of Dronabinol Oral Solution development (IND 75228) the Controlled Substance Staff (CSS) advised that Dronabinol Oral Solution may not have the same abuse potential as Marinol (Schedule III), the oral capsule, because of different formulation characteristics. Dronabinol Oral Solution is formulated in water and ethanol contained in a glass container having a total of 150 mg of dronabinol per 30 ml of solution. In contrast, Marinol is formulated in a manner that vitiates the abuse potential of its active pharmaceutical ingredient (API) in that it is dissolved in sesame oil and encapsulated in soft gelatin capsules. CSS recommended to the Sponsor when Dronabinol Oral Solution is filed under a NDA 505 (b)(2) application having Marinol, a Schedule III drug, as the reference drug, the abuse potential of the new formulation must be characterized. Even if the two drug products contain the same API, the abuse potential of the proposed oral solution is not the same as that of Marinol (Schedule III) capsules formulated in sesame oil. Scheduling of the oral solution is based upon the evaluation of all data related to the abuse potential of the new formulation.

Further, CSS informed the Sponsor in November 2012 of the need for a Human Abuse Potential Study to be conducted for Dronabinol Oral Solution. CSS specifically indicated that a human abuse potential study will provide data on the abuse potential of Dronabinol Oral Solution (Schedule I) relative to that of Marinol capsules (Schedule III) following single dose administration. Dronabinol Oral Solution needs to be tested in cannabinoid-preferring individuals at the proposed therapeutic dose, as well as at safe higher doses (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.

Given that dronabinol itself is a Schedule I substance, the product containing dronabinol is appropriately placed into a schedule of the Controlled Substances Act upon approval of an NDA, depending upon data considered that relate to the abuse potential of the new product. Thus, relevant results in the abuse potential study of the two products are compared and appropriately weighed with other considerations, specifically in vitro chemical studies described above.

Study Design

Clinical Trial INS-13-017 was a single-dose, randomized, double-blind, double-dummy, placebo and active-controlled, 5-way crossover study. Each subject participated in a medical screening visit, a Qualification (drug discrimination) visit, 5 Treatment periods, and a Follow-up visit. Within approximately 45 days of a standard medical screening, subjects attended a randomized, double-blind Qualification visit in which they received 20 mg Marinol and matching placebo in a randomized crossover manner to ensure that they could discriminate the positive effects of the comparator. The Qualification visit involved a 5-night (6-day) inpatient stay in the research clinic. Admission to the Qualification visit occurred on Day -2 (2 days before the first dosing). Subjects were dosed with 20 mg Marinol or placebo on Days 1 and 3. A washout day (Day 2) was imposed between dosing days such that each dose was separated by at least 48 hours. Subjects were discharged on Day 4, approximately 24 hours after the second dose was received, at the discretion of the investigator or designee.

Eligible subjects were then enrolled in the Treatment phase, which consisted of five 3-night (4-day) inpatient stays in the research clinic. The last drug administration in the Qualification phase and the first drug administration in the Treatment phase were separated by a washout interval of at least 8 days.

During the 5 treatment periods, subjects received single oral doses of each of the following treatments in a randomized, double-blind, crossover manner:

- Placebo oral solution + Marinol 10 mg
- Placebo oral solution + Marinol 30 mg
- Dronabinol Oral Solution 10 mg + Marinol placebo
- Dronabinol Oral Solution 30 mg + Marinol placebo
- Placebo oral solution + Marinol placebo

Drug administration in each treatment period was separated by a washout interval of 8 to 21 days. Subjects returned for an end-of-study safety follow-up visit 5 to 10 days after the last drug administration in the Treatment phase.

The primary objective of Study INS-13-017 was to evaluate the abuse potential of Dronabinol Oral Solution compared to Marinol (dronabinol capsule) and placebo in recreational cannabinoid users. The secondary objective was to assess the safety and tolerability of single oral doses of Dronabinol.

The primary PD endpoint in this study was Emax on Drug Liking VAS.

The secondary PD endpoints were:

- Balance of effects:

-Drug Liking VAS (minimum score [Emin] and time-averaged area under the effect curve [TA_AUE]
-Overall Drug Liking VAS (Emax and Emin)
-Take Drug Again VAS (Emax)
-SDV (Emax)

- Positive effects:

-High VAS (Emax and TA_AUE)
-Good Effects VAS (Emax and TA_AUE)
-Stoned VAS (Emax and TA_AUE)

- Negative effects:

-Bad Effects VAS (Emax and TA_AUE)

- Sedative effects:

-Alertness/Drowsiness VAS (Emax and TA_AUE)

- Other effects:

-Any Effects VAS (Emax and TA_AUE)

-Other summary parameters included the time to maximum effect [TEmax] and/or time to minimum effect [TEmin]. These summary parameters were calculated, as appropriate, for all measures except for Overall Drug Liking VAS, Take Drug Again VAS, and subjective drug value (SDV).

The following safety endpoints were evaluated:

- Incidence, frequency and severity of AEs
- Clinical laboratory assessments (hematology, chemistry, urinalysis)
- Vital signs (heart rate, sitting BP, respiratory rate, oral temperature)
- Physical examination results
- 12-lead ECG

Study Population

About 85 subjects were planned to be randomized to the Qualification phase in order to randomize approximately 40 subjects to the Treatment phase, with the intent to ensure evaluable data from at least 30 subjects. Healthy male and female subjects 18 to 55 years of age, inclusive, were recruited by one center in Canada (INC Research Toronto).

Inclusion Criteria for participation were standard but included the following criteria that are relevant for a cannabinoid human abuse potential study:

- Body mass index (BMI) within the range of 18.0 to 33.0 kg/m2, inclusive, and a minimum weight of 50.0 kg
- Current recreational cannabinoid users who had used cannabinoids (e.g., smoked marijuana or hashish or oral THC) at least once a week (on average) during the 3 months prior to Screening and at least 4 times in a given week in the 3 months prior to Screening

Exclusion Criteria are standard but included the following criteria that are relevant for a cannabinoid human abuse potential study:

- Substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders - Fourth Revision (DSM-IV), and/or subjects who had ever been in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence
- History of syncope within 3 months prior to Screening or any history of recurrent and/or unexplained episodes of syncope.
- Any history of epilepsy or seizures (except childhood febrile seizures)
- History of cardiac disorder within 3 months prior to Screening
- Any history (including family history) of schizophrenia or other psychotic illness
- Use of a prohibited medication (i.e., a prescription, non-prescription, herbal or natural health product).
- History of active tuberculosis (TB). Contact with an active TB case within 2 years prior to screening. Lived in or visited a country with a high TB incidence. Positive for latent TB infection

Subjects were required to pass the following qualification criteria to be eligible to enter the Treatment phase:

- Peak score (Emax) in response to 20 mg Marinol ≥60 on Drug Liking VAS and greater than that of placebo (difference of at least 15 points).
- Acceptable placebo response on Drug Liking VAS (i.e., score from 40 to 60, inclusive).

Treatment Phase

During the Treatment phase, the Dronabinol Oral Solution, Marinol encapsulated capsules, and placebos (placebo oral solution and placebo encapsulated tablets) were administered using a double-dummy procedure to maintain blinding.

Subjects received the following treatments orally during the Treatment phase:

- *Treatment A:* Placebo oral solution (2 mL and 6 mL doses of placebo oral solution) + 10 mg Marinol (1x 10 mg encapsulated capsule and 2x placebo encapsulated tablets)
- *Treatment B:* Placebo oral solution (2 mL and 6 mL doses of placebo oral solution) + 30 mg Marinol (3x 10 mg encapsulated capsules)
- *Treatment C:* 10 mg Dronabinol Oral Solution (one 2 mL dose of Dronabinol Oral Solution and one 6 mL dose of placebo oral solution) + 3 placebo encapsulated tablets
- *Treatment D:* 30 mg Dronabinol Oral Solution (one 2 mL dose of placebo oral solution and one 6 mL dose of Dronabinol Oral Solution) + 3 placebo encapsulated tablets
- *Treatment E:* Placebo oral solution (2 mL and 6 mL doses of placebo oral solution) + 3 placebo encapsulated tablets

Disposition of Study Subjects

Of the 43 subjects who were randomized to the Treatment phase, 33 subjects (76.7%) were included in the PD population. This consisted of those subjects who received all 5 treatments and had no major protocol violations. Ten subjects (23.3%) were excluded from the PD population because they were withdrawn prior to completing all treatment periods of the study. The demographics and baseline characteristics of the PD population are summarized in **Table 3**.

Table 3 Demographic and Baseline Characteristics of Randomized Population

Characteristic	Safety Population N=43
Age (years)*	
Mean (SD)	36.0 (8.84)
Min, Max	21, 55
Sex, n (%)	
Male	37 (86.0%)
Female	6 (14.0%)
Race, n (%)	
White	32 (74.4%)
Black or African American	5 (11.6%)
Asian	5 (11.6%)
Other 1	1 (2.3%)
BMI (kg/m2)	
Mean (SD)	26.0 (2.53)
Min, Max	20.9, 31.9

BMI=body mass index; SD=standard deviation *Age at informed consent. Percentage is calculated based on the number of subjects in the Safety Population as the denominator.

A total of 43 subjects completed the Qualification Phase and were randomized in the Treatment Phase. Of these, 33 subjects (76.7%) completed all 5 treatment periods of the study. A total of 10 subjects (23.3%) discontinued from the study prior to completion. The reasons for discontinuation are detailed in **Table 4**.

A major protocol deviation occurred during the Qualification Phase related to study restrictions for meal content. The lemonade served at dinner on Day 1 (10 hours post-dose) and at lunch on Day 3 (4 hours post-dose) contained white grapefruit pulp. Grapefruit or grapefruit juice can inhibit cytochrome P450 (CYP) 3A4 in the gastrointestinal tract and THCs (including dronabinol) undergo extensive first-pass metabolism and are substrates of CYP 3A4. The deviation was considered by the Sponsor to have had a minimal potential impact on the bioavailability of dronabinol (20 mg Marinol), which was administered in a randomized manner with placebo on either Day 1 or Day 3 of the Qualification Phase. Consumption of lemonade with grapefruit pulp occurred at least 10 hours after the first dose administration on Day 1 and at least 4 hours after dose administration on Day 3 (i.e., after the majority of the oral absorption process of dronabinol was expected to be completed). Consequently, the impact on the PD and safety assessments performed after the deviations occurred was deemed by the Sponsor to be minimal.

One subject (Subject 9082) performed pre-dose PD assessments 19 minutes post-dose in error; this time point was excluded from all analyses. There was no effect on the primary endpoint because Drug Liking VAS was not collected at pre-dose, and the pre-dose time point was considered missing for the secondary measures High VAS, Stoned VAS and Alertness/Drowsiness VAS.

Table 4 Reasons for Discontinuation during the Treatment Phase

	Placebo (N=39) n(%)	Marinol 10 mg (N=35) n(%)	Marinol 30 mg (N=37) n(%)	Dronabinol Oral Soln. 10 mg (N=36) n(%)	Dronabinol Oral Soln. 30 mg (N=40) n(%)	TOTAL (N=43) n(%)
Number of subjects who withdrew early	3(7.7)	0	3(8.1)	1(2.8)	3(7.5)	10(23.3)
Reasons for withdrawal: AE	0	0	2(5.4)	0	1(2.5)	3(7.0)
Withdrawal by subject	2 (5.1)	0	0	1 (2.8)	0	3 (7.0)
Lost to follow-up	0	0	0	0	0	0
Administrative reasons	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0
Physician decision	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Non-compliance	0	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0	0
Other	1 (2.6)	0	1 (2.7)	0	2 (5.0)	4 (9.3)

AE=adverse event Percentage is calculated based on the number of subjects treated for each treatment or overall (N) as the denominator.

No subject was discontinued during the Treatment Phase due to a protocol deviation. There were 16 protocol deviations during the Treatment phase. There were no major protocol deviations and all protocol deviations were considered by the Sponsor to be minor. There were 9 protocol deviations

related to PD assessments during the Treatment phase. Protocol deviations during the Treatment Phase are shown in **Table 5**.

Table 5 Protocol Deviations during the Treatment Phase

	Placebo (N=39)	Marinol 10 mg (N=35)	Marinol 30 mg (N=37)	Dronabinol Oral Soln. 10 mg (N=36)	Dronabinol Oral Soln. 30 mg (N=40)
All Categories Total	3	3	3	3	4
Missed Procedures/Assessments:					
Clinical Laboratory Tests	0	1	1	0	0
Vital Signs	0	0	1	0	1
Procedures/Assessments Outside Protocol Window:					
Electrocardiogram	0	1	0	0	1
Pharmacodynamic Assessments (PD)	3	0	1	3	2
Study Restrictions: Clinical Laboratory Tests	0	1	0	0	0

Pharmacodynamic Results

Results of Qualification Phase

All subjects included in the PD Population met the PD Qualification criteria. The subjects' Drug Liking VAS Emax values for 20 mg Marinol were ≥60 (range: 75-100) and showed differences of at least 15 points greater than placebo. All subjects showed appropriate placebo responses between 40 and 60 (range: 50-55). Overall, the mean and median placebo Emax values at the neutral point (50.5 and 50.0, respectively) and high Emax values with Marinol (95.9 and 100.0, respectively) indicate that the subject

population was appropriate for inclusion in the study (PD Population). The Qualification Phase results for the primary endpoint (Drug Liking VAS Emax) are shown in **Table 6**.

Table 6 Drug Liking VAS Emax Results for the Qualification Phase (PD Population)

	Placebo N=33	Marinol 20 mg N=33
Mean (SD)	50.5 (0.94)	95.9 (6.78)
Median	50.0	100.0
Range	50-55	75-100

Emax=maximum effect; PD=pharmacodynamic; range=minimum, maximum; SD=standard deviation; VAS=visual analog scale

Results of Treatment Phase

Primary Endpoint

Drug Liking VAS Emax values were close to neutral (50) with placebo, higher with 10 mg Marinol and 10 mg Dronabinol Oral Solution, and highest with the 30 mg doses of Marinol and Dronabinol Oral Solution. Median T Emax was 0.5 hours with placebo and ranged from approximately 2 to 3 hours with Marinol and 1.5 to 2 hours with Dronabinol Oral Solution. Minimal effects were observed on Drug Liking VAS Emin; values were close to neutral for placebo and active treatments (median of 50.0 for all treatments). Compared to Emax, active treatment-related effects on Drug Liking VAS TA_AUE were less pronounced relative to placebo; however, the pattern of results was similar to Emax, with similar effects between comparable doses of Marinol and Dronabinol Oral Solution. By-subject data for derived parameters for Drug Liking VAS are summarized in **Table 7**.

Table 7 Selected Descriptive Statistics of Derived Parameters for Drug Liking VAS

Endpoint/ Statistic	Placebo (N=33)	Marinol 10 mg (N=33)	Marinol 30 mg (N=33)	Dronabinol Oral Soln. 10 mg (N=33)	Dronabinol Oral Soln. 30 mg (N=33)
Emax					
Mean (SD)	54.2 (10.12)	78.1 (19.08)	89.0 (13.30)	81.4 (16.18)	91.7 (11.51)
Median	51.0	75.0	96.0	83.0	100.0
T Emax (h)					
Median	0.500	2.983	2.000	2.000	1.500
Range	0.48, 12.00	0.50, 24.00	1.00, 12.00	0.50, 4.00	0.50, 12.00
Emin Mean (SD)	48.3 (8.69)	45.5 (12.61)	45.6 (11.43)	47.3 (9.71)	46.5 (9.22)
Median	50.0	50.0	50.0	50.0	50.0
T Emin (h)					
Median	0.500	0.500	0.500	0.500	0.500
Range	0.48, 24.00	0.48, 24.00	0.48, 24.00	0.48, 24.00	0.48, 24.00
TA_AUE					
Mean(SD)	49.90 (2.879)	55.83 (10.064)	60.00 (9.779)	55.86 (13.899)	60.30 (10.050)
Median	50.02	53.05	57.30	53.16	56.30

Emax=maximum effect; Emin=minimum effect; h=hour; N=number of subjects; PD=pharmacodynamic; range=minimum, maximum; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; TEmax/min=time to peak effect; VAS=visual analog scale

A statistically significant overall treatment effect was observed for the Drug Liking VAS Emax primary endpoint. Pairwise comparisons showed statistically significant differences between both doses of Marinol and placebo. No statistically significant differences were observed between comparable doses of Marinol and Dronabinol Oral Solution (10 mg vs 10 mg; 30 mg vs 30 mg), while consistent with its similarity to Marinol, Dronabinol Oral Solution also showed statistically greater Drug Liking VAS Emax compared with placebo.

While Drug Liking VAS Emin (secondary endpoint) did not show a statistically significant overall treatment effect, TA_AUE (secondary endpoint) showed results consistent with Emax. All active treatments had effects that were statistically greater than placebo, while no statistically significant

differences were observed between comparable doses of Marinol and Dronabinol Oral Solution. These results are demonstrated in **Table 8**.

Table 8 Analysis Results for Drug Liking VAS Emax and TA_AUE

	Emax *(Primary Endpoint)*		**TA_AUE** *(Secondary Endpoint)*	
	Median Difference	**P Value**	**Median Difference**	**P Value**
Overall Treatment Effect	—	<0.001	—	<0.001
Marinol vs Placebo				
Marinol 10 mg-Placebo	24.0	<0.00	1 3.05	<0.001
Marinol 30 mg-Placebo	38.0	<0.001	7.30	<0.001
Dronabinol Oral Solution vs Marinol				
Dronabinol 10mg-Marinol 10 mg	0.0	0.340	-0.21	0.784
Dronabinol 30mg-Marinol 30 mg	0.0	0.107	-0.03	0.923
Dronabinol Oral Solution vs Placebo				
Dronabinol 10 mg-Placebo	27.0	<0.001	3.69	<0.001
Dronabinol 30 mg-Placebo	43.0	<0.001	6.22	<0.001

Emax=maximum effect; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

The mean scores over time for Drug Liking VAS are illustrated in the Sponsor's figure, Figure 1.

While mean placebo scores remained near neutral, responses to 10 mg of Dronabinol Oral Solution and Marinol were higher and showed peak effects between 2 to 3 hours post-dose and a return to neutral by 8 hours post-dose. The higher dose (30 mg) of both Dronabinol Oral Solution and Marinol showed higher and slightly earlier peak effects (1.5 and 2 hours, respectively), as well as a slightly longer duration (up to 12 hours post-dose). There was a higher and earlier peak for 10 mg Dronabinol Oral Solution than for 10 mg Marinol, as well as an earlier peak for 30 mg Dronabinol Oral Solution than Marinol.

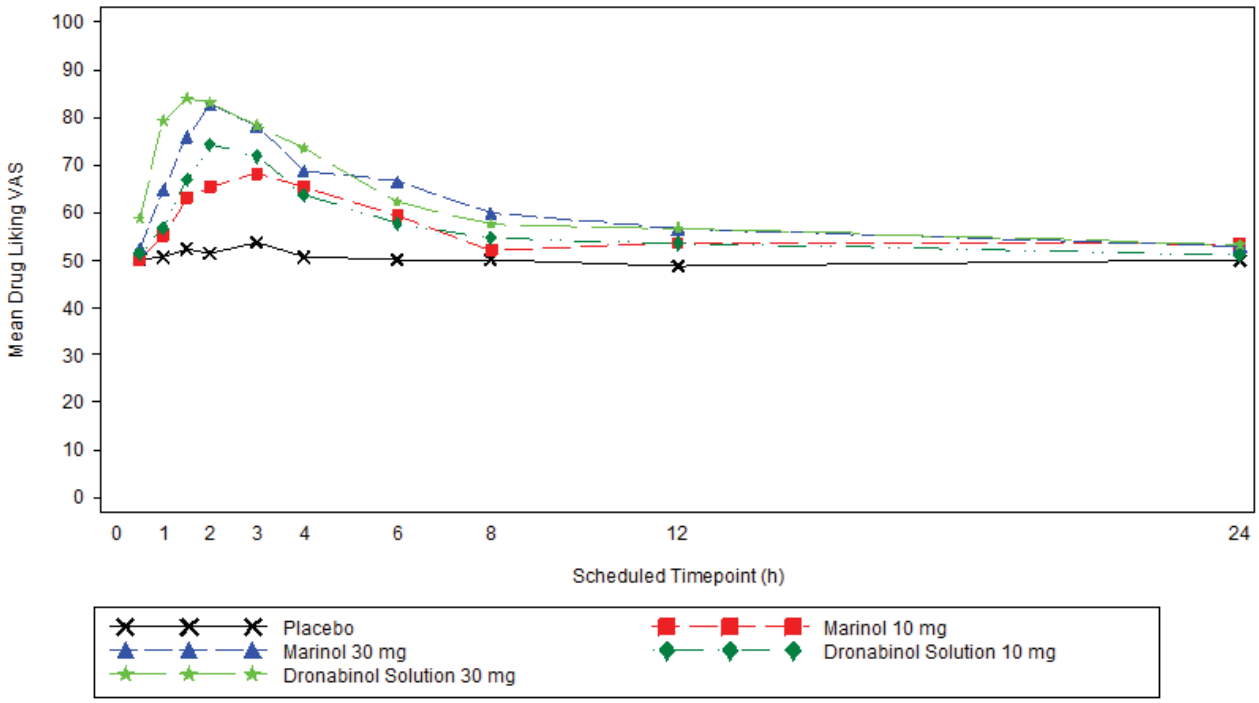


Figure 1- Mean Drug Liking VAS Scores over Time
PD=pharmacodynamic; VAS=visual analog scale Responses range from 0 (Strong disliking) to 100 (Strong liking) with neutral point 50 (Neither like nor dislike).

Secondary Endpoints

Balance of Effects

As with Drug Liking VAS, secondary Overall Drug Liking VAS, Take Drug Again VAS, and SDV measures (Emax) showed minimal effects of placebo. Although in some cases mean or median Emax values were slightly higher with similar doses of one treatment vs another (i.e., slightly higher median values with 30 mg Marinol vs 30 mg Dronabinol or vice versa for the 10 mg dose), overall, the effects of Marinol and Dronabinol were very similar on these global measures. End-of-day/next-day Overall Drug Liking VAS Emin values were higher for active treatments compared to placebo and showed relatively similar scores across all active treatments.

Statistically significant overall treatment effects were observed for all end of- day/next-day secondary balance of effects endpoints. Pairwise comparisons were consistent across all endpoints and confirmed

that while both Marinol and Dronabinol showed statistically significantly greater effects compared to placebo, there were no statistically significant differences between comparable doses of the two treatments (10 mg vs 10 mg and 30 mg vs 30 mg). To maintain the blind between Marinol and the placebo to Marinol, Marinol capsules and placebo tablets were enclosed in identical empty gelatin capsules on site prior to dose administration. To maintain the blind between Dronabinol Oral Solution and placebo oral solution, each dose was administered as 3 oral syringes. The 2 mL (10 mg at 5 mg/mL) dose was administered as one 2 mL syringe. The 6 mL (30 mg) dose was divided into two 3 mL syringes. These treatment effects are summarized in **Table 9**.

Table 9 Selected Descriptive Statistics of Derived Parameters for Secondary End-of-Day/Next-Day Balance of Effects Measures

Endpoint/Statistic	**Placebo** N=33	**Marinol** 10 mg N=33	**Marinol** 30 mg N=33	**Dronabinol Oral Soln.** 10 mg N=33	**Dronabinol Oral Soln.** 30 mg N=33
Overall Drug Liking VAS					
Emax Mean (SD)	52.4 (9.64)	77.7 (19.82)	87.5 (15.55)	81.0 (21.31)	84.8 (17.09)
Median	50.0	80.0	95.0	86.0	86.0
Emin Mean (SD)	50.0 14.17)	73.5 (22.71)	76.4 (21.60)	75.8 (21.20)	77.0 (24.31)
Median	50.0	72.0	80.0	80.0	80.0
Taking Drug Again VAS					
Emax Mean (SD)	10.4 (25.19)	69.8 (37.70)	86.8 (18.39)	79.3 (32.01)	84.6 (19.02)
Median	0.0	89.0	97.0	93.0	88.0
Subjective Drug Value (SDV)					
Emax Mean (SD)	1.36 (3.57)	17.82 (3.57)	25.21 (15.53)	18.35 (14.22)	26.80 (15.12)
Median	0.25	15.00	26.75	13.75	26.75

Emax=maximum effect; Emin=minimum effect; N=number of subjects; PD=pharmacodynamic; SD=standard deviation; VAS=visual analog scale

A summary of analysis results for Take Drug Again VAS Emax, SDV Emax and Overall Drug Liking VAS are provided, respectively, in **Table 10**. Statistically significant overall treatment effects were observed for all end of- day/next-day secondary balance of effects endpoints. Pairwise comparisons were consistent across all endpoints and confirmed that while both Marinol and Dronabinol Oral Solution showed statistically significantly greater effects compared to placebo, there were no

statistically significant differences between comparable doses of the two treatments (10 mg vs 10 mg and 30 mg vs 30 mg).

Table 10 Analysis Results for Secondary End-of-Day/Next-Day Balance of Effects Measures

	Overall Drug Liking VAS				**Take Drug Again VAS**		**Subjective Drug Value**	
	Emax		***Emin***		***Emax***		***Emax***	
	Med. Diff.	P Value	Med. Diff.	P Value	Med. Diff.	P Value	Med. Diff.	P Value
Overall Treatment Effect	-	<0.001	-	<0.001	-	<0.001	-	<0.001
Marinol vs Placebo								
Marinol 10 mg-Placebo	23.0	<0.001	20.0	<0.001	71.0	<0.001	13.500	<0.001
Marinol 30 mg-Placebo	44.0	<0.001	35.0	<0.001	90.0	<0.001	26.500	<0.001
Dronabinol Oral Solution vs Marinol								
Dronabinol 10mg-Marinol 10 mg	0.0	0.244	0.0	0.604	0.0	0.249	0.00	0.504
Dronabinol 30mg-Marinol 30 mg	0.0	0.535	0.0	0.855	0.0	0.686	0.00	0.496
Dronabinol Oral Solution vs Placebo								
Dronabinol 10 mg-Placebo	32.0	<0.001	30.0	<0.001	85.0	<0.001	13.500	<0.001
Dronabinol 30 mg-Placebo	35.0	<0.001	35.0	<0.001	86.0	<0.001	26.500	<0.001

Emax=maximum effect; Emin=minimum effect; PD=pharmacodynamic; VAS=visual analog scale
Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

At 12 hours post-dose, the mean effects of Marinol and Dronabinol Oral Solution 10 mg were slightly lower than those of the 30 mg doses; however, the effects at 24 hours post-dose were more similar between all 4 active treatments. The mean Overall Drug Liking VAS at 12 and 24 hour post-dose are shown in the Sponsor's figure, **Figure 2**.

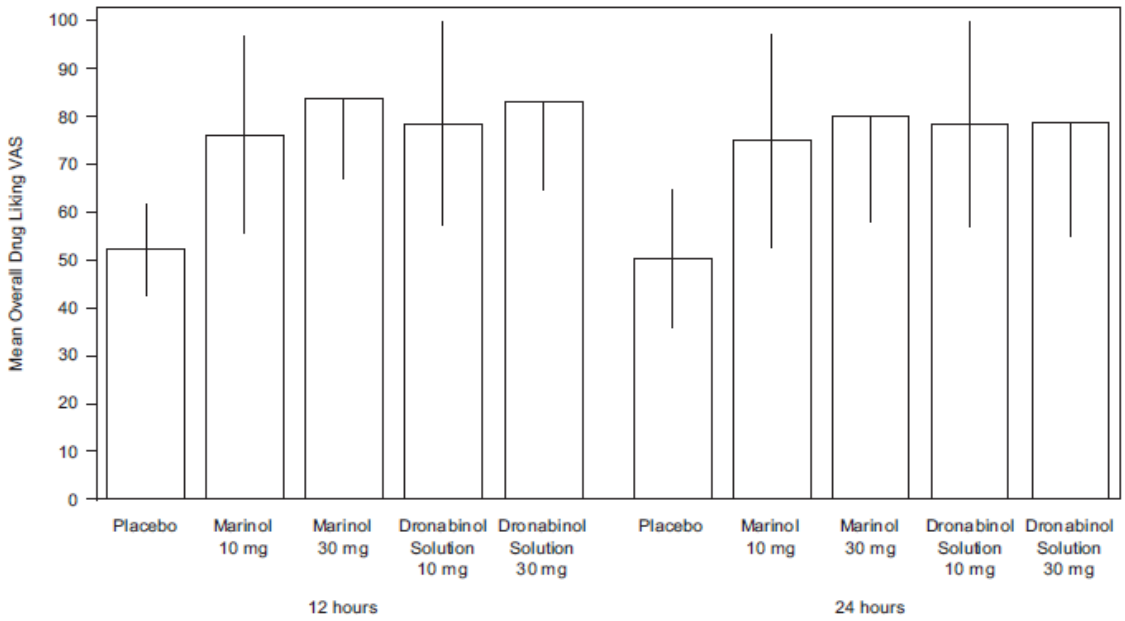


Figure 2 Mean Overall Drug Liking VAS at 12 and 24 Hours Post-Dose
PD=pharmacodynamic; VAS=visual analog scale Responses range from 1 (Strong disliking) to 100 (Strong liking) with neutral point 50 (Neither like nor dislike). If the error bands extend above the upper limit (100) or lower limit (0), then that half is not shown.

Positive Effects

The derived parameters of secondary positive effects measures, including High VAS, Good Effects VAS, and Stoned VAS are summarized in **Table 11**. The results were similar across all secondary positive effects measures. Placebo was associated with scores at or close to neutral (0), while both Marinol and Dronabinol Oral Solution showed increasing effects with increasing dose, although mean Emax of Stoned VAS showed relatively low scores with both of the 10 mg doses. Across all measures, median TEmax was 0.5 hours with placebo, 2.0 hours with Marinol (both doses) and 10 mg Dronabinol Oral Solution and 1.5 hours with 30 mg Dronabinol Oral Solution. While TA_AUE values for the 3 measures showed lesser effects, the pattern of results was similar to Emax, with similar values observed for comparable doses of Marinol and Dronabinol Oral Solution.

Table 11 Selected Descriptive Statistics of Derived Parameters for Secondary Positive Effects Measures

Endpoint/ Statistic	Placebo (N=33)	Marinol 10 mg (N=33)	Marinol 30 mg (N=33)	Dronabinol Oral Solution 10 mg (N=33)	Dronabinol Oral Solution 30 mg (N=33)
Good Effects VAS					
E max Mean (SD)	121 (26.60)	66.7 (31.77)	89.0 (17.22)	74.9 (28.10)	89.5 (13.36)
E max Median	0.0	73.0	96.0	85.0	96.0
TEmax (h)Median	0.500	2.000	2.000	1.983	1.500
TEmax Range	0.48, 6.00	0.48, 6.00	1.00, 8.00	0.50, 3.02	0.50, 6.00
TA_AUE Mean(SD)	2.99 (9.410)	14.35 (19.072)	23.83 (17.668)	14.75 (17.064)	24.09 (14.949)
TA_AUE Median	0.00	8.23	23.64	9.32	19.31
High VAS					
Emax Mean (SD)	10.0 (21.98)	60.5 (33.01)	85.8 (17.90)	67.3 (28.10)	88.8 (15.28)
Emax Median	0.0	65.0	90.0	74.0	97.0
TEmax (h) Median	0.500	2.000	2.067	2.000	1.500
TEmax (h) Range	0.48, 3.00	0.48, 6.00	1.00, 6.00	0.50, 3.02	1.00, 4.00
TA_AUE Mean(SD)	1.13 (3.596)	10.42 (12.557)	19.68 (12.989)	11.09 (11.766)	19.89 (11.904)
TA_AUE Median	0.00	6.58	18.93	8.27	18.44
Stoned VAS					
Emax Mean (SD)	5.0 (15.92)	53.0 (36.55)	81.1 (26.81)	55.9 (33.05)	84.4 (20.93)
Emax Median	0.0	65.0	91.0	63.0	95.0
TEmax (h) Median	0.500	2.000	2.000	1.983	1.500
TEmax Range	0.48, 6.00	0.48, 6.00	1.00, 6.00	0.50, 3.02	0.50, 6.00
TA_AUE Mean(SD)	0.85 (3.482)	8.93 (10.626)	18.40 (11.598)	9.39 (10.210)	18.67 (11.575)

TA_AUE Median	0.00	6.13	18.99	5.39	17.71

Emax=maximum effect; h=hour; N=number of subjects; PD=pharmacodynamic; Range=minimum, maximum; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; TEmax=time to peak effect; VAS=visual analog scale

Overall treatment effects were statistically significant for all secondary positive effects endpoints; results of the pairwise comparisons were consistent across all endpoints and with the primary endpoint and other balance of effects measures. Specifically, while both doses of Marinol and Dronabinol Oral Solution showed statistically greater effects compared to placebo, no statistically significant differences were observed between comparable doses of Marinol and Dronabinol Oral Solution (10 mg vs 10 mg or 30 mg vs 30 mg) on any of the endpoints. These treatment effects are summarized in **Table 12**.

Table 12 Analysis Results for Secondary Positive Effects Measures

	Good Effects VAS				**High VAS**				**Stoned VAS**			
	Emax		***TA_AUE***		***Emax***		***TA_AUE***		***Emax***		***YA_AUE***	
	Median Diff.	**P**	**Median Diff.**	**P**	**Median Diff.**	**P**	**Median Diff.**	**P**	**Median Diff.**	**P**	**Median Diff.**	**P**
Overall Treatment Effect	—	<0.001	—	<0.001	—	<0.001	—	<0.001	—	<0.001	—	<0.001
Marinol 10 mg-Placebo	66.0	<0.001	7.78	<0.001	54.0	<0.001	5.55	<0.001	60.0	<0.001	5.07	<0.001
Marinol 30 mg-Placebo	86.0	<0.001	16.99	<0.001	85.0	<0.001	14.96	<0.001	85.0	<0.001	18.79	<0.001
Dronabinol Oral Solution 10mg-Marinol 10 mg	0.0	0.256	-0.32	0.466	0.0	0.204	-0.19	0.949	0.0	0.743	-0.08	0.553
Dronabinol Oral Solution 30 mg-Marinol 30 mg	0.0	0.920	-0.45	0.951	0.0	0.316	1.12	0.463	0.0	0.538	0.65	0.841
Dronabinol Oral Solution 10 mg-Placebo	68.0	<0.001	6.66	<0.001	63.0	<0.001	5.53	<0.001	62.0	<0.001	4.52	<0.001

Dronabinol Oral Solution 30 mg-Placebo	85.0	<0.001	18.14	<0.001	91.0	<0.001	16.71	<0.001	87.0	<0.001	16.86	<0.001

Emax=maximum effect; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

The mean good effects VAS scores over time are presented in the Sponsor's figure, Figure 2. Similar to Drug Liking VAS (at this moment), mean scores on secondary positive effects measures showed minimal effects of placebo, higher scores with the lower doses of both active treatments (10 mg), and prominent effects of the 30 mg dose of both treatments. Peak effects of all active treatments occurred between 1.5 hours and 3 hours post-dose, although the effects of 30 mg Dronabinol tended to peak slightly earlier compared to the other active treatments. Effects of all treatments returned to baseline by 12 hours post-dose.

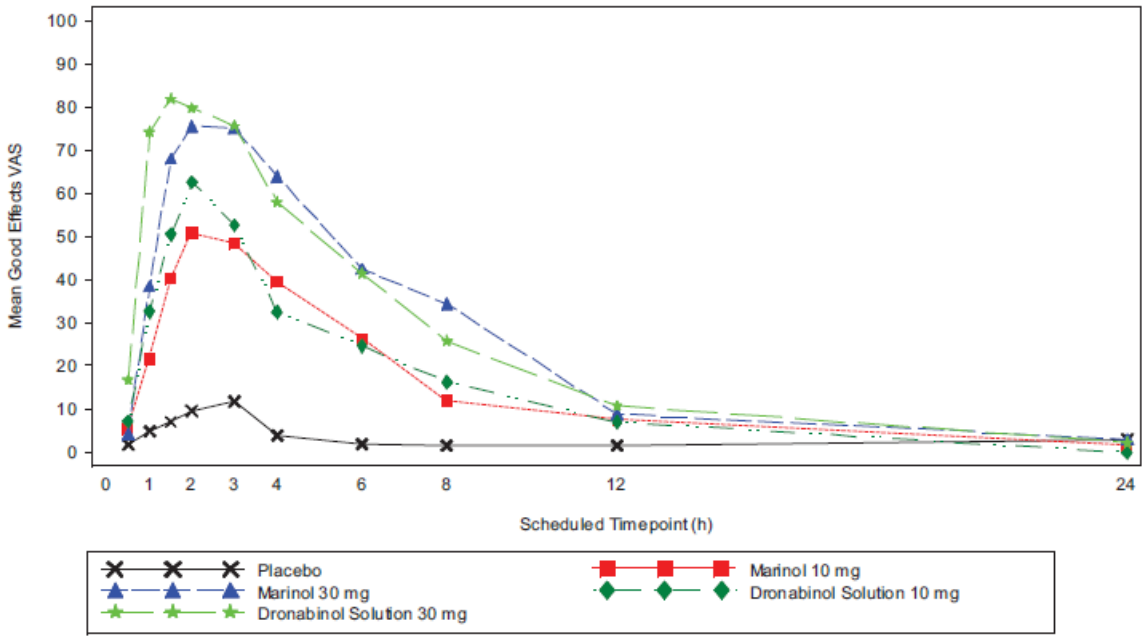


Figure 2 Mean Good Effects VAS Scores over Time
PD=pharmacodynamic; VAS=visual analog scale Responses range from 0 (Not at all) to 100 (Extremely).Negative Effects.

A total of 36 subjects (of 43 subjects in the Randomized Population) had one or more outliers; 17 had outliers on only 1 or 2 endpoints for a given treatment. A few subjects had outliers only with placebo, and results indicating higher than usual responses across multiple measures. A few subjects had outliers only to Marinol (and in some cases also placebo), mostly indicating slightly lower responses. Of the remaining subjects with outliers to at least one Dronabinol Oral Solution dose, most of these showed lower responses. A few subjects had outlying high responses to Dronabinol Oral Solution; however, these subjects also had high responses across multiple treatment periods, including placebo. Overall, the individual subject outlier data did not indicate any subsets of subjects with unusually high

responses to Dronabinol Oral Solution

Negative effects

Bad Effects VAS Emax and TA_AUE values showed minimal effects of treatment although mean Emax scores were slightly higher with the active treatments compared to placebo and with the 30 mg doses compared to the 10 mg doses. Median TEmax values were 0.5 hours post-dose for placebo and both 10 mg doses, 1.5 hours for 30 mg Marinol, and about 2 hours for 30 mg Dronabinol. These are demonstrated in **Table 13.**

Table 13 Selected Descriptive Statistics of Derived Parameters for Bad Effects VAS

		Marinol		**Dronabinol Oral Solution**	
Endpoint/ Statistic	**Placebo** N=33	**10 mg** N=33	**30 mg** N=33	**10 mg** N=33	**30 mg** N=33
Emax Mean (SD)	4.6 (15.22)	13.1 (24.45)	25.6 (31.69)	16.1 (27.53)	22.8 (29.29)
Emax Median	0.0	0.0	12.0	0.0	6.0
TEmax (h) Median	0.500	0.500	1.500	0.500	1.983
TEmax (h) Range	0.48, 3.00	0.48, 24.00	0.48, 12.00	0.48, 6.02	0.48, 12.00
TA_AUE Mean (SD)	2.06 (9.151)	2.74 (7.497)	4.56 (8.471)	1.49 (3.513)	3.53 (7.159)
TA_AUE Median	0.00	0.00	0.62	0.00	0.51

Emax=maximum effect; h=hour; N=number of subjects; PD=pharmacodynamic; Range=minimum, maximum; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; TEmax=time to peak effect; VAS=visual analog scale

A summary of Bad Effects VAS Emax and TA_AUE are provided in **Table 14**. Statistically significant overall treatment effects were observed for both Bad Effects VAS endpoints. Bad Effects VAS Emax and TA_AUE values were statistically greater with all active treatments compared with placebo, with the exception of TA_AUE for 10 mg Marinol. Comparable doses of Marinol and Dronabinol Oral Solution (10 mg and 10 mg; 30 mg and 30 mg) were not statistically different.

Table 14 Analysis Results for Bad Effects VAS

	Emax		TA_AUE	
	Median Difference	**P Value**	**Median Difference**	**P Value**
Overall Treatment Effect	—	<0.001	—	<0.001
Marinol 10 mg-Placebo	0.0	0.012	0.00	0.119
Marinol 30 mg-Placebo	12.0	<0.001	0.62	0.003
Dronabinol Oral Solution 10 mg-Marinol 10 mg	0.0	0.763	0.00	0.511
Dronabinol Oral Solution 30 mg-Marinol	0.0	0.424	0.00	0.378
Dronabinol Oral Solution 10 mg-Placebo	0.0	0.012	0.00	0.024
Dronabinol Oral Solution 30 mg-Placebo	5.0	<0.001	0.46	0.003

Emax=maximum effect; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

Sedative and Other Effects

Alertness/Drowsiness VAS and Any Effects VAS derived parameters are summarized in **Table 15**. These showed the effects of the active treatments consistent with both increases in alertness (higher Emax values) and increases in drowsiness (lower Emin values) compared with placebo. Overall, effects were similar between Marinol and Dronabinol Oral Solution at comparable doses. In general, median TEmax occurred earlier than TEmin with the active treatments (1.5 to 2 hours vs 3 hours with Marinol and 1 to 1.5 hours vs 2 to 3 hours with Dronabinol Oral Solution). Presumably, because of the opposing effects of the active treatments on Alertness/Drowsiness, VAS, and TA_AUE, values were close to 50

(neutral) for all treatments. Any Effects VAS showed results similar to the positive effects measures, with similar scores observed between comparable doses of Marinol and Dronabinol Oral Solution. Median TEmax was 0.5 hours with placebo, about 2 hours with Marinol doses and Dronabinol Oral Solution 10 mg, and 1.5 hours with the 30 mg of Dronabinol Oral Solution.

Table 15 Selected Descriptive Statistics of Derived Parameters for Drowsiness/Alertness VAS

Endpoint/ Statistics		**Marinol**		**Dronabinol Oral Solution**	
	Placebo (N=33)	**10 mg** (N=33)	**30 mg** (N=33)	**10 mg** (N=33)	**30 mg** (N=33)
Alert/Drowsiness VAS					
Emax Mean (SD)	60.4 (17.16)	70.0 (19.05)	75.0 (19.87)	71.2 (19.29)	76.5 (17.74)
Emax Median	51.0	64.0	75.0	66.0	75.0
TEmax (h) Median	0.500	2.000	1.500	1.500	1.000
TEmax (h) Range	0.48, 24.00	0.48, 24.00	0.48, 24.00	0.50, 24.00	0.50, 24.00
Emin Mean (SD)	44.7 (16.49)	34.6 (17.23)	30.2 (23.19)	35.8 (19.25)	28.6 (22.77)
Emin Median	50.0	39.0	27.0	37.0	35.0
TEmin (h)	0.500	3.000	3.000	2.000	2.983
TEmin (h)	0.48, 8.00	0.48, 24.00	0.48, 12.00	0.48, 6.00	0.50, 8.00
TA_AUE Mean (SD)	54.20 (11.137)	51.83 (10.370)	51.73 (13.939)	52.55 (12.266)	51.71 (15.560)
TA_AUE Median	50.08	50.25	50.04	50.74	50.36
Any Effects VAS					
Emax Mean (SD)	8.6 (20.04)	63.9 (34.59)	89.9 (17.90)	72.4 (27.58)	90.4 (13.15)
Emax Median	0.0	69.0	96.0	80.0	100.0
TEmax (h) Median	0.500	2.000	2.000	1.983	1.500
TEmax Range	0.48, 3.00	0.48, 6.02	1.00, 4.00	0.50, 4.00	0.50, 4.00
TA_AUE Mean (SD)	1.22 (3.801)	12.88 (16.213)	25.27 (19.052)	13.32 (16.303)	25.02 (15.515)

TA_AUE Median	0.00	8.41	24.76	6.93	19.50

Emax=maximum effect; Emin=minimum effect; N=number of subjects; PD=pharmacodynamic; SD=standard deviation; TA_AUE=time averaged area under the effect curve; TEmax/min=time to peak effect; VAS=visual analog scale.

Alertness/Drowsiness VAS Emax, Emin, and TA_AUE and Any Effects VAS Emax and TA_AUE are summarized in **Table 16**. Statistically significant overall treatment effects were observed for Alertness/Drowsiness VAS Emax and Emin and both Any Effects VAS endpoints, but not Alertness/Drowsiness VAS TA_AUE. Consistent with the other subjective measures, both doses of Marinol and Dronabinol Oral Solution showed statistically greater effects relative to placebo, while no statistically significant differences were observed between comparable doses of Marinol and Dronabinol Oral Solution on any of the endpoints.

Table 16 Analysis Results for Alertness/Drowsiness VAS Emax and Emin

	Alertness/Drowsiness VAS				Any Effects VAS			
	Emax		*Emin*		*Emax*		*TA_AUE*	
	LS Mean Difference	P Value	Median Difference	PValue	Median Difference	PValue	Median Difference	PValue
Overall Treatment	—	<0.001	—	<0.001	—	<0.001	—	<0.001
Marinol 10 mg-Placebo	11.1	<0.001	-4.0	0.005	66.0	<0.001	7.15	<0.001
Marinol 30 mg-Placebo	14.9	<0.001	-8.0	<0.001	94.0	<0.001	19.17	<0.001
Dronabinol 10 mg-Marinol 10 mg	1.4	0.635	0.0	0.927	0.0	0.322	-1.16	0.533
Dronabinol 30 mg-Marinol 30 mg	0.4	0.901	0.0	0.393	0.0	0.895	-1.02	0.993
Dronabinol 10 mg-Placebo	12.5	<0.001	-3.0	<0.001	65.0	<0.00	1 5.43	<0.001
Dronabinol 30 mg-Placebo	15.2	<0.001	-12.0	<0.001	96.0	<0.001	19.15	<0.001

Emax=maximum effect; Emin=minimum effect; LS=least squares ; PD=pharmacodynamic; TA_AUE=time-averaged area under the effect curve; VAS=visual analog scale a LS means were estimated from a mixed-effect model having treatment, period, treatment sequence and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as:
a covariate, and subject nested within sequence as a random effect.
b Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

Any Effects VAS showed strong effects of the active treatments with a slightly earlier onset with Dronabinol Oral Solution. There was still a similar duration of both active treatments (until 12 hours postdose). This is demonstrated in the Sponsor's figure, Figure 3.

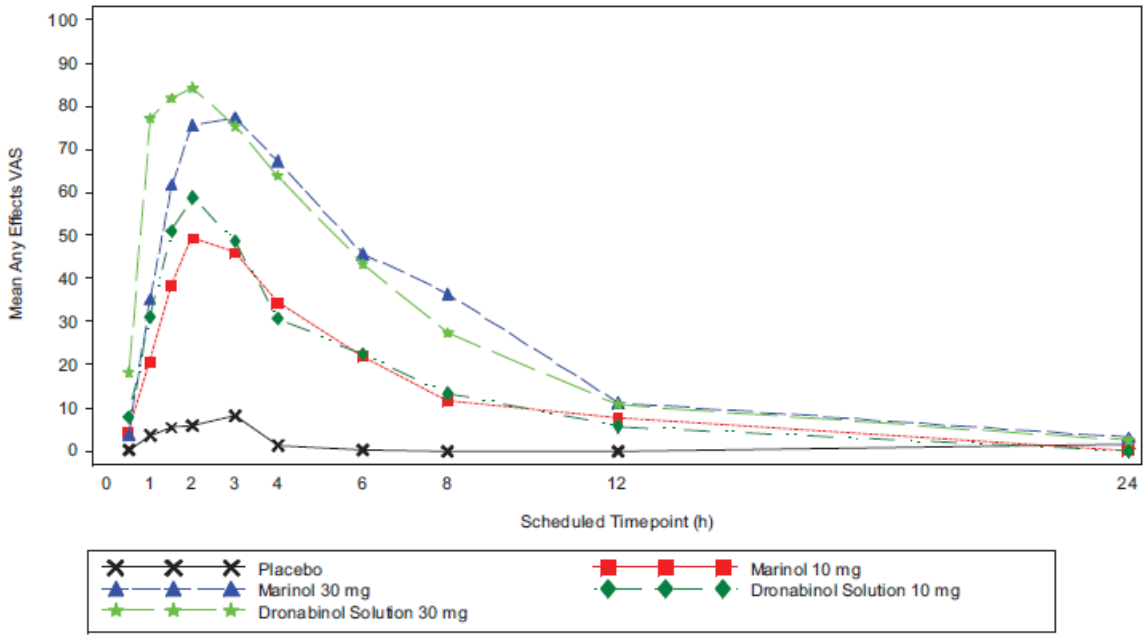


Figure 3 Mean Any Effects VAS Scores over Time
PD=pharmacodynamic; VAS=visual analog scale Responses range from 0 (Not at all) to 100 (Extremely).

Assessment of Study INS-13-017 Data, Confirmed by Dr. Wei Liu's Statistical Conclusions

This study confirms the Sponsor's assertion that the abuse liability of Dronabinol Oral Solution (10 mg and 30 mg) is essentially the same as the positive control Marinol (10 mg and 30 mg), based on the pre-defined primary and key secondary endpoints: peak effects of Drug Liking (at the moment) and High VAS, areas under VAS curves during the treatment period, Overall Drug Liking measured using VAS (at 12-h and 24-h post-dose in treatment phase), and Take Drug Again measured using VAS (at 12-h and 24-h post-dose in treatment phase). The differences between Marinol at either high or low dose and Dronabinol Oral Solution at either high or low dose are not statistically significant in the primary and key secondary PD endpoints.

In summary, Dronabinol Oral Solution and Marinol demonstrated statistically significant abuse-related subjective effects compared to placebo. There were no statistically significant differences between comparable doses of Marinol and Dronabinol Oral Solution on any of the primary or key secondary endpoints. These results confirm that Dronabinol Oral Solution has subjective abuse potential comparable to that of Marinol in recreational cannabis users when taken as prescribed in this dose range. Unfortunately, the PD of sublingual Dronabinol Oral Solution was not addressed in this HAPS study. Both alcohol and THC are readily absorbed sublingually raising the potential for another abuseable route of administration of Dronabinol Oral Solution which would not be possible with Marinol.

2.2. Clinical Risks and Adverse Reactions.

2.2.1. Labeled warnings and adverse reactions

Current Marinol label [redacted] includes warnings about the occurrence of [redacted]; syncope, tachycardia, hypotension and hypertension; multiple substance abuse, psychiatric disorders, and central nervous system reactions.

Regarding adverse reactions, the most common adverse reactions to dronabinol are dizziness, euphoria, paranoid reaction, thinking abnormal, abdominal pain, and vomiting.

The following paragraph summarized the information provided under Warning and Precautions section (Section 5) of the Marinol [redacted]

- [redacted]
- *Syncope, Tachycardia, Hypotension, and Hypertension* - The label warns that patients with cardiac disorders may experience occasional hypotension, possible hypertension, syncope, or tachycardia when using dronabinol
- *Multiple Substance Abuse* – The label warns that patients with a history of substance abuse, including alcohol abuse or dependence may be more prone to abuse dronabinol as well.
- *Psychiatric Disorders*- [redacted] may exacerbate mania, depression, or schizophrenia and that patient suffering these illnesses should receive careful psychiatric monitoring.
- *Central Nervous System Reactions*- Additive or synergistic effects may be experienced by patients on concomitant therapy with sedatives, hypnotics, or other psychoactive drugs. [redacted]

2.2. 2. Abuse Potential of the formulation and risks associated with overdose

Dronabinol is the generic name given to the (-) Delta-9-*trans* isomer of tetrahydrocannabinol (delta-9-THC) of synthetic origin. It is present in marijuana and considered the primary psychoactive constituent in marijuana (Gaoni and Mechoulam, 1964) and is currently a Schedule I substance.

Dronabinol Oral Solution contains dronabinol, the same active pharmaceutical ingredient (API) as that found in the FDA approved Marinol capsules (Schedule III), and both products are indicated for the treatment of the same conditions. However, Dronabinol Oral Solution is controlled under Schedule I of the Controlled Substances Act (CSA) given that its primary active drug, synthetic delta-9-THC, is listed as a Schedule I substance [21 CFR 1308.11(d)(30)] and that a solution of dronabinol does not meet the

criteria specified under 21 CFR 1308.13 (g) (1) to be controlled under Schedule III of the CSA. Upon approval, Dronabinol Oral Solution will be placed in a different schedule.

Dronabinol Oral Solution and Marinol capsules have the same pharmacology and similar pharmacokinetics. However, these formulations differ in their chemistry. Formulation differences account for a different abuse potential, because the formulation may have a direct effect on the route of abuse, the population abusing the product, on patterns of abuse and on expected adverse effects associated with the ways the product is abused.

In vitro studies were conducted by the Sponsor of the New Drug Application for the Dronabinol Oral Solution (Insys Pharmaceuticals) to explore the ease with which the product could be manipulated with the purpose of obtaining dronabinol containing extracts that could be smoked, taken intranasally or intravenously, in comparison to Marinol capsules. These studies demonstrate that Dronabinol Oral Solution can be successfully manipulated to afford highly concentrated extracts of dronabinol that can be abused by smoking or through other routes of abuse. In addition, in vitro studies further demonstrate that the Dronabinol Oral Solution is more vulnerable to manipulation than the Marinol capsules, which is used as a comparison in these studies. Therefore, it is more likely that Dronabinol Oral Solution will be targeted for abuse than the Marinol capsules, indicating that the solution has a higher potential for abuse than the 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 relative bioavailability of the solution to the Marinol capsule (150 mg bioequivalent to 176 mg of dronabinol capsules) adds to the risk of adverse outcomes and of unintentional overdose from abuse when taken through the oral route. In addition, the perceived risks associated with drinking 30 mL of an alcoholic solution may be different to 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. Additionally, although not assessed by the Sponsor, the Dronabinol Oral Solution product would be readily absorbed sublingually. This raises the potential for another abuseable route of administration of Dronabinol Oral Solution which would not be possible with Marinol.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) was reported by patients receiving dronabinol capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving dronabinol capsules. About 25% of patients reported a CNS adverse reaction during the first 2 weeks and about 4% reported such a reaction each week for the next 6 weeks thereafter.

Overdose with dronabinol products is described in the Marinol and Dronabinol Oral Solution labels as including signs and symptoms of drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth, tachycardia, memory impairment, depersonalization, mood alteration, urinary retention, reduced bowel motility, decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders. In case of an overdose, the current label recommends (b) (4)

[redacted] (b) (4) (Section 10, Overdosage, Marinol and Dronabinol Oral Solution Label)

There is not much data available in the literature to evaluate the safety consequences of taking large amounts of delta -9-THC when taking marijuana, as marijuana smokers tend to self-titrate to the desired psychoactive effects. Eating marijuana tends to produce a delayed, stronger and longer lasting "high" than smoking and individuals cannot predict the effects of an oral dose of delta-9-THC. One of the reasons for this difference is due to a difference in the way delta-9-THC is metabolized when smoked versus taken orally. When dronabinol is taken orally the onset of effects is delayed because its absorption is slower than when smoked (with mean time to peak plasma concentration (Tmax) at 1-2 hours after ingestion in contrast with 5-10 minutes to peak plasma concentration (Tmax) if smoked). In addition, when taken orally a larger amount of the active metabolite, 11-hydroxy-delta-9-THC is produced than when taken through the intravenous or smoking routes. This metabolite is approximately equipotent to dronabinol in producing cannabinoid-like subjective effects (Agurell et al., 1986, Lemberger and Rubin, 1975).

In the State of Colorado, where there is a wide variety of products infused with delta-9-THC, policymakers have considered imposing caps on all recreational edibles at 10 mg delta-9-THC (one tenth of the currently allowed levels). The high-content delta-9-THC-containing edibles became a source of concern due to two cases that were reported in the public domain. In one case, a student visiting Denver jumped from a hotel balcony after eating a multi-serving marijuana-infused cookie that was estimated to contain 65 mg of THC (National Conference of State Legislature, 2015, Nicks, 2104). Hancock-Allen et al., 2014, reported that in this case, an autopsy performed 29 hours after the time of death found marijuana intoxication as a chief contributing factor, cannabinoids (7.2 ng/mL delta-9-THC and 49 ng/mL delta-9-carboxy-THC, an inactive marijuana metabolite) being the only drugs present. The authors concluded that this case represented the first reported death in Colorado since the approval of recreational use of marijuana by the state in 2012 that is linked to marijuana consumption without evidence of poly-substance use. In the second case, a man shot and killed his wife while allegedly hallucinating after eating a marijuana-laced product. However, in this case no further information is available. These cases illustrate a potential risk to the public health associated with the recreational ingestion of large amounts of delta-9-THC.

3. Regulatory issues and assessment

Dronabinol Oral Solution is controlled under Schedule I of the Controlled Substances Act (CSA) given that its primary active drug, synthetic delta-9-THC, is listed as a Schedule I substance [21 CFR 1308.11(d)(30)] and that a solution of dronabinol does not meet the criteria specified under 21 CFR 1308.13 (g) (1) to be controlled under Schedule III of the CSA.

Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Considering that upon approval Dronabinol Oral Solution will have a

recognized medical use and could be safely used under medical supervision, the product will be rescheduled from Schedule I and placed in a different schedule.

The Sponsor claims that based on the similar chemistry and pharmacology to that of Marinol capsules their product should be placed in Schedule III of the CSA. However, based on data from in vitro studies these formulations differ in their chemistry. Formulation differences may account for a different abuse potential, because the formulation may have a direct effect on the route of abuse, the population abusing the product, and on patterns of abuse and expected adverse effects associated with the ways the product is abused.

At the time of approval of Marinol in 1985, the abuse potential of this formulation was considered high, and the product was rescheduled from Schedule I to Schedule II based on its accepted medical use and high abuse potential (51FR 17476). However, in 1999, in response to a DEA request that followed the filing of a petition from Unimed Pharmaceutical, Inc., Marinol capsules were rescheduled from Schedule II to III. The basis of the request was the petitioner's view that there was a lack of actual abuse of the drug product during its years of marketing. Upon consideration by the Assistant Secretary for Health of the Department of Health and Human Services (ASH, HHS), the DEA rescheduled the product from Schedule II to Schedule III, based on the lack of actual abuse and the difficulty in separating the active ingredient from the formulation, which may limit the possible abuse of the formulation through the inhalation route.

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/s/

SILVIA N CALDERON
02/26/2016

MICHAEL KLEIN
02/26/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: February 11, 2016

To: Maureen Dewey, MPH
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205525
OPDP Comments for draft Syndros (dronabinol) oral solution, CIII PI and carton labeling

OPDP has reviewed the proposed draft Syndros (dronabinol) oral solution, CIII PI and carton labeling, retrieved from SharePoint on February 9, 2016, and have no additional comments. Comments on the patient labeling will be submitted under a separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI & carton labeling.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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

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

/s/

MEETA N PATEL
02/11/2016

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

Pharmacovigilance Memorandum

Date:	January 6, 2016
Reviewer(s):	Nicholas Miles, PharmD, Safety Evaluator Division of Pharmacovigilance-I (DPV-I)
Team Leader(s):	Eileen Wu, PharmD, Team Leader Division of Pharmacovigilance-I (DPV-I)
Division Director(s):	Robert L. Levin, MD, Division Director Division of Pharmacovigilance-I (DPV-I) Cindy Kortepeter, PharmD, Deputy Division Director (Acting) Division of Pharmacovigilance-I (DPV-I)
Product Name(s):	Marinol (dronabinol capsule)
Subject:	QT prolongation
Application Type/Number:	NDA 018651
Applicant/Sponsor:	Abbvie, Inc.
OSE RCM #:	2015-2450

Reference ID: 3869903

1 INTRODUCTION

The purpose of this memorandum is to provide DGIEP a brief analysis of the postmarketing data in the FDA Adverse Event Reporting System (FAERS) database regarding any potential signal for a risk of QT prolongation and related events (such as Torsades de pointes) with dronabinol capsules (NDA 018651).

2 BACKGROUND

On July 15, 2015, the CDER Division of Cardiovascular and Renal Products (DCRP) QT Interdisciplinary Review Team (QT-IRT) was consulted to assess the QT effect of dronabinol based on a 2013 thorough QT (TQT) study conducted by Sellers et. al., evaluating the QT effects of tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray. The QT-IRT concluded the TQT study was not adequate based on several limitations:

1. The doses studied were not adequate to cover the therapeutic exposure for the antiemetic indication.
2. The ECG assay sensitivity was questionable because a typical QTc time course for the moxifloxacin treatment arm was not demonstrated.
3. There were inconsistent results presented in the paper.

Therefore, the QT-IRT reported the results of the 2013 TQT study conducted by Sellers et. al. would not be able to be applied to dronabinol oral solution. The QT-IRT recommended conducting an additional QT study to assess the QT effect of dronabinol oral solution at the upper limit of the antiemetic dosing range. [1]

On November 4, 2015, at the mid-cycle meeting for dronabinol oral solution (NDA 205525), DPV-I presented a postmarketing analysis of dronabinol capsule (NDA 018651). In the review, DPV-I evaluated all cases since 2006 and did not identify a safety signal for QT prolongation.[2] Considering the recommendation from the QT-IRT and the finding from the DPV-I postmarketing safety analysis, Dr. Joette Meyer, Associate Director of labeling with the Division of Gastroenterology and Inborn Errors Products (DGIEP), requested the Division of Pharmacovigilance-I (DPV-I) to assess the risk of QT prolongation with dronabinol capsules using data from the FAERS database since approval.

The results of this assessment of the FAERS cases will assist DGIEP in determining whether NDA 205525 will require a Thorough QT Study (TQT) with dronabinol to evaluate the risk of QT prolongation.

3 METHODS AND MATERIALS

DPV-I searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	November 9, 2015
Time Period of Search	May 31, 1985 † - November 9, 2015
Search Type	FBIS quick query

Reference ID: 3869903

Product Terms	Product active ingredient: dronabinol‡
MedDRA Search Terms (Version 18.0)	Broad Scope - Standardized MedDRA Queries (SMQ): Torsades de pointes, shock-associated conditions Torsades de pointes/QT prolongation

* See Appendix A for a description of the FAERS database.

† US Approval date

‡ Dronabinol and THC are linked in the FAERS drug product dictionary; therefore, our search contained reports associated with illegal and legal marijuana use.

4 RESULTS

4.1 SUMMARY OF OVERALL SAFETY PROFILE

The FAERS search described in Table 1 retrieved 83 reports. Table 2 summarizes descriptive characteristics of the 83 FAERS reports.

Table 2. Descriptive Characteristics of FAERS Reports of QT prolongation and Related Events for Dronabinol Capsules received by FDA from May 31, 1985 – November 9, 2015

		(N=83)*
Sex	Male	52
	Female	30
	Unknown	1
Country	United States	69
	Foreign	13
	Not Reported	1
Report type	Expedited	78
	Direct	2
	Periodic	3
Serious Outcomes^	Death	40
	Life-threatening	10
	Hospitalized	42
	Disability	2
	Congenital anomaly	0
	Other serious	46

* May include duplicates.

^ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcome.

Table 3 summarizes the most frequently reported MedDRA Preferred Terms (PTs) for the 83 FAERS reports.

Reference ID: 3869903

Table 3. Most Frequently Reported MedDRA PTs for Reports of QT prolongation and Related Events with Dronabinol Capsules, received by FDA from May 31, 1985 – November 9, 2015, sorted by decreasing number of FAERS reports per PT Total Number of Reports* = 83		
Row	**MedDRA PT**	**Number of FAERS Reports**
1	Loss of Consciousness	24
2	Cardiac Arrest	15
3	Cardio-respiratory Arrest	13
4	Respiratory Failure	8
5	Syncope	7
6	Acute Kidney Injury	5
7	Renal Failure	5
8	Anuria	4
9	Circulatory Collapse	4
10	Electrocardiogram QT Prolonged	4
11	Acute Respiratory Failure	2
12	Hepatic Congestion	2
13	Multi-organ Failure	2
14	Hypoperfusion	1
15	Sudden Death	1
16	Ventricular Arrhythmia	1
17	Ventricular Fibrillation	1
18	Ventricular Tachycardia	1
* A report may contain more than one preferred term.		

4.2 SUMMARY OF KEY FINDINGS

This section summarizes the reports in aggregate. These summaries use crude counts of reports and may contain duplicate reports.

The FAERS search retrieved 83 reports, with 18 reports citing the use of dronabinol. Approximately 78% (65/83) of the reports documented positive blood or urine tetrahydrocannabinol (THC) levels without stating the use of dronabinol. Of those, 61 were related to overdoses of multiple substances, including THC, benzodiazepines, opiates, illegal substances, and alcohol. It is important to note that the majority of the reports also listed an opiate or benzodiazepine as a suspect product.

4.2.1 Overview of Reports with a Death Outcome

There were 40 reports with an outcome of death. The most commonly reported PTs were cardiac arrest, respiratory arrest, or both. Benzodiazepines, opiates (including methadone), illegal substances, and alcohol were the most commonly reported co-suspect drugs in these reports. Many reports documented post-mortem blood or urine THC levels without mentioning dronabinol. Among the two death cases that did not involve polysubstance use, one described a 71-year-old woman who developed syncopal episodes following administration of dronabinol

capsules. Her death was attributed to disease progression of acute myeloid lymphoma (FAERS Case # 10908527). Another report described a 63-year-old female who developed palpitations following dronabinol administration for appetite stimulation; her death was attributed to advancement of cancer (FAERS Case # 6368815).

4.2.2 Selected Event of Interest

Drug interactions

FAERS Case # 8602243, USA, 2012: A 55-year-old female ovarian cancer patient experienced electromechanical dissociation following administration of dronabinol capsules, doxorubicin hydrochloride, and zolpidem tartrate.

Reviewer comment: This case was highlighted because it presents a possible drug interaction between dronabinol, doxorubicin hydrochloride, and zolpidem that resulted in electromechanical dissociation. Doxorubicin hydrochloride and zolpidem tartrate have (b) (4).

FAERS Case # 7157116, USA, 2010: This is a literature case. A 56-year-old white male was hospitalized with a diagnosis of an upper gastrointestinal bleed. Upon admission, his international normalized ratio (INR) was 10.41 and hemoglobin level was 6.6 g/dL. He received 4 units of fresh frozen plasma and one 10 mg dose of oral vitamin K; his INR improved to 1.8 the next day. The patient was discharged seven days after admission. However, he was readmitted 15 days after discharge with a constant nosebleed and increased bruising. His INR value was 11.55 and hemoglobin was 13.9 g/dL. During this hospitalization, the patient experienced a syncopal episode upon standing. After treatment, he was discharged with an INR value of 1.14. The patient reported smoking marijuana more frequently (approximately 4-5 joints per week) between these two hospitalizations due to his depression. After counseling and education, the patient decided to stop smoking marijuana. After discontinuation of marijuana, his INR values ranged from 1.08 to 4.4 with no significant bleeding complications for a nine-month period. The authors suspect the adverse events were related to a drug interaction between warfarin, clopidogrel, and marijuana. Past medical history included esophageal reflux, coronary artery disease, peripheral vascular disease, two coronary artery stents placed, and seizure disorder. Past surgical history included placement of a cardiac pacemaker and mechanical heart valve replacement approximately 11 years prior to the hospitalization. Concurrent medications included furosemide 40 mg daily, metoprolol 12.5 mg twice daily, potassium chloride 20 mEq daily, tramadol 50 mg every 6 hours as needed for pain, carbamazepine sustained action 200 mg daily, valproic acid 250 mg twice daily, sertraline 50 mg daily, omeprazole 20 mg daily, clopidogrel 75 mg daily, and aspirin 81 mg daily.

Reviewer comment: This literature case was highlighted because it presents a possible drug interaction between warfarin, clopidogrel and THC. The patient experienced a syncopal episode upon standing; syncope is a labeled event for dronabinol.

4.2.3 Selected Preferred Terms of Interest

Reports for selected Preferred Terms are summarized below. We included loss of consciousness, syncope, and sudden death because they are of interest to DGIEP.

Loss of consciousness (PT, Table 3, Row 1) (n=24)

Of the 24 reports, 19 were associated with positive blood or urine THC levels without mention of dronabinol. Eighteen of the 19 reports involved polysubstance overdose. The reports described patients overdosing on a multitude of legal or illegal substances, including benzodiazepines, opiates (such as methadone), muscle relaxants, heroin, acetaminophen, aspirin, and alcohol. The remaining report with a positive THC level (source unspecified) described a 47-year-old man who lost consciousness while driving that lead to a traffic accident. The patient was taking gabapentin, oxcarbazepine, oxycodone, amitriptyline, and THC for trigeminal neuralgia. Five of 24 reports specifically list dronabinol capsule, but three had no temporal association. The remaining two reports are summarized below.

FAERS Case # 6180798, USA, 2006: A physician reported a 62-year-old male overdosed on dronabinol capsules (amount unknown), which led to unconsciousness and resulted in a fall. The patient was taking dronabinol to treat depression. He was hospitalized for a possible cervical fracture and required respiratory support. The patient discontinued dronabinol capsules; however, the patient remained hospitalized, requiring respiratory support. Past medical history and concomitant medications were not reported.

FAERS Case # 7070886, USA, 2009: A pharmacist reported a 31-year-old male patient who experienced nausea, abdominal pain, and "felt funny" with dronabinol. The patient was taking dronabinol 5 mg three times daily. On October 1, 2008, the patient initiated dronabinol therapy for an unknown indication. Following administration on the first day, the patient reported to the pharmacist that he experienced flatulence, abdominal pain, and nausea. On the second day after administration, the patient reported that he "blacked out" for an unknown duration. The patient did not seek medical attention; however, he took diphenhydramine for symptom relief and felt better within the hour. The patient reported to the pharmacist that the symptoms occur sporadically month-to-month. The patient discontinued dronabinol in July 2009. Following drug discontinuation, all reported adverse events were ongoing except for the "blacked out" episodes.

Syncope (PT, Table 3, Row 5) (n=7)
Of the seven reports, four were associated with positive blood or urine THC levels without mention of dronabinol. Two of the four reports described patients overdosing on a multitude of legal or illegal substances, including benzodiazepines, opiates (such as methadone), muscle relaxants, heroin, acetaminophen, aspirin, and alcohol. The third report described a 70-year-old man who developed a syncopal episode following the administration of sildenafil and THC. The action taken in response to the syncopal episode for sildenafil and THC and the outcome of the syncopal episode were not reported. The fourth report that described a syncopal episode upon standing (a labeled event) is summarized in Section 3.2.2. Of the 3 reports that specifically listed dronabinol capsule, one described a 71-year-old woman who developed syncopal episodes following administration of dronabinol capsules. Her death was attributed to disease progression of acute myeloid lymphoma (also mentioned in Section 4.2.1). The second report described a male patient of unknown age who "passed out and was taken to the hospital" following an accidental ingestion of dronabinol 30 mg. The patient was dispensed the wrong medication. The third report described a 58-year-old who experienced "dizziness and fainting" following administration of dronabinol for treatment of chemotherapy-induced nausea and vomiting.

Electrocardiogram QT Prolonged (PT, Table 3, Row 10) (n=4)
All four reports were associated with positive blood or urine THC levels without mention of dronabinol. These reports described patients overdosing on a multitude of legal or illegal substances, including benzodiazepines, opiates (such as methadone), muscle relaxants, heroin, acetaminophen, aspirin, and alcohol.

Sudden Death (PT, Table 3, Row 15) (n=1)
This is a report associated with a positive blood THC level without mention of dronabinol. This report described a 23-year-old male patient who died in a motor vehicle accident while taking alprazolam, cocaine, THC, and ethanol.

Ventricular arrhythmia (PT, Table 3, Row 16) (n=1)
This report described a 33-year-old male patient who died from a multidrug overdose, resulting in a ventricular dysrhythmia. The autopsy report revealed the patient had carisoprodol, oxycodone, and THC in his system. There was no mention of dronabinol.

Ventricular fibrillation (PT, Table 3, Row 17) (n=1)
This report described a 22-year-old male patient who was found unresponsive with no detectable pulse from an overdose of droperidol. The autopsy report revealed the patient had phencyclidine and THC in his system. There was no mention of dronabinol.

Ventricular tachycardia (PT, Table 3, Row 18) (n=1)
This report described a 26-year-old male patient who died from a multidrug overdose. The autopsy report revealed the patient had morphine, alprazolam, nortriptyline, codeine, and THC in his system. There was no mention of dronabinol.

5 DISCUSSION AND CONCLUSION

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 (See Appendix B for a list of MedDRA Preferred Terms within the SMQs).

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.

6 REFERENCES

1. Stockbridge, N. CDER Division of Cardiovascular and Renal Products QT Interdisciplinary Review Team Consult to NDA 205525. (Internal Report). October 2015. Reference ID: 3838628.
2. Miles, N. CDER DPV Postmarketing Safety Analysis of Marinol (dronabinol capsule). (Internal Report). November 2015. Reference ID: 3849448.

7 APPENDIX A

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8 APPENDIX B

MedDRA Preferred Terms within the SMQs

Table 4. MedDRA PTs within the SMQs	
PTs within Torsades de pointes, shock-associated conditions SMQ	**PTs within Torsades de pointes/QT prolongation SMQ**
Circulatory collapse	**Electrocardiogram QT interval abnormal**

Reference ID: 3869903

Electrocardiogram QT interval abnormal	**Electrocardiogram QT prolonged**
Electrocardiogram QT prolonged	**Long QT syndrome**
Long QT syndrome	**Long QT syndrome congenital**
Long QT syndrome congenital	**Torsade de pointes**
Torsade de pointes	**Ventricular tachycardia**
Ventricular tachyarrhythmia	Cardiac arrest
Ventricular tachycardia	Cardia death
Acute kidney injury	Cardiac fibrillation
Acute prerenal failure	Cardio-respiratory arrest
Acute respiratory failure	Electrocardiogram repolarisation abnormality
Anuria	Electrocardiogram U-wave abnormality
Blood pressure immeasurable	Loss of consciousness
Cerebral hypoperfusion	Sudden cardiac death
Grey syndrome neonatal	Sudden death
Hepatic congestion	Syncope
Hepatojugular reflux	Ventricular arrhythmia
Hepatorenal failure	Ventricular fibrillation
Hypoperfusion	Ventricular flutter
Jugular vein distension	Ventricular tachyarrhythmia
Multi-organ failure	
Myocardial depression	
Neonatal anuria	
Neonatal multi-organ failure	
Neonatal respiratory failure	
Organ failure	
Prerenal failure	
Propofol infusion syndrome	
Renal failure	
Renal failure neonatal	
Respiratory failure	
Please note: PTs in bold are narrow scope, meaning they are more likely associated with the event of interest.	

9 APPENDIX C

Line Listing of Cases (n=83)

FAERS Case Number	Version Number	Manufacturer Control Number
10027047	3	US-ABBVIE-14P-163-1213261-00
10208763	1	US-BRISTOL-MYERS SQUIBB COMPANY-20862611
10549539	2	US-ABBVIE-14P-163-1299150-00
10747677	2	ADR-2015-00192
10908527	1	N/A
10963601	1	DE-JNJFOC-20150315071
11054467	1	NSR_02044_2015

11062800	1	DE-TEVA-555375GER
11159629	1	US-ABBVIE-14P-163-1281408-00
11202431	1	SE-RECKITT BENCKISER PHARMACEUTICAL, INC-RB-080344-2015
11558235	1	PA-PFIZER INC-2015312131
3154288	1	801703002
3264055	1	9917851
3539193	2	200556
3712515	3	2014247
3738388	1	DRON00201004844
3806818	1	USA-2002-0000806
3865329	1	N/A
4028634	1	KII-2003-0004091
4028695	1	KII-2003-0004021
4029003	1	KII-2003-0004013
4042252	1	2003-03843
4061673	2	2003164678US
4063723	1	KII-2003-0006631
4112745	1	04H-163-0252513-00
4126479	1	KII-2004-0009251
4150430	1	KII-2004-0010386
4164972	1	KII-2004-0011418
4168154	1	KII-2004-0011612
4177594	1	DRON00204000324
4178466	1	DRON00204002327
4199866	1	KII-2004-0013087
4212134	1	USA-2002-0000689
5759095	1	KII-2005-0015322
5822240	1	KII-2005-0016832
5824425	1	KII-2005-0016886
5859551	1	KII-2005-0017643
5884242	1	KII-2005-0018594
5888746	13	PHEH2005US10715
5941196	1	KII-2005-0019847
5953236	1	KII-2005-0020172
5960543	1	KII-2005-0020453
5985234	1	KII-2006-0020908
6180798	1	US-SOLVAY-00206003988
6188210	1	KII-2003-0009816
6220605	1	DE-SOLVAY-00207000184
6272263	2	USA-2006-0025348
6368815	5	CA-SOLVAY-00307033316
6543733	1	US-PFIZER INC-2008007763
6650895	3	US-PURDUE-USA 2008 0033052
6745233	1	KADN20080310

6812110	2	AT-PURDUE-DEU_2008_0004825
7070886	2	US-SOLVAY-00209004102
7157116	2	US-BAYER-200935391GPV
7331875	1	US-ROXANE LABORATORIES, INC.-2010-RO-00323RO
7331877	1	US-ROXANE LABORATORIES, INC.-2010-RO-00297RO
7361107	1	KADN20100070
7769537	2	US-JNJFOC-20110103987
7929637	1	US-JNJFOC-20110411256
7929871	1	US-JNJFOC-20110411128
8013736	1	PHHY2011AU56197
8324241	1	US-PAR PHARMACEUTICAL, INC-2011SCPR003674
8351546	1	IMP 05707 2012
8410771	3	US-ASTELLAS-2012US000319
8602243	1	US-JNJFOC-20120521516
9011288	1	US-PFIZER INC-2013004256
9027447	1	US-PAR PHARMACEUTICAL, INC-2013SCPR005304
9033139	1	US-FRI-1000041977
9034074	1	AUR-APL-2013-00202
9063785	1	US-RB-044123-12
9069124	1	US-BANPHARM-20130764
9101657	1	US-COVIDIEN/TYCO HEALTHCARE/MALLINCKRODT-T201300512
9113643	1	CHPA2013US002585
9120616	1	US-ROCHE-1193938
9138602	1	IMP_06242_2013
9145475	1	2013020041
9145926	1	2013020133
9321507	1	2013P1006239
9813885	1	US-PFIZER INC-2014006140
9854557	1	US-PAR PHARMACEUTICAL, INC-2014SCPR008648
9855364	1	CA-JNJFOC-20140116854
9883065	1	IMP_07212_2014
9973113	1	US-FRI-1000054805

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/s/

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M E M O R A N D U M

From: Erica L. Wynn MD, MPH, Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Acting Director,
Division of Pediatric and Maternal Health (DPMH)
CDER/Office of New Drugs/ODEIV

To: Division of Gastroenterology and Inborn Error Products (DGIEP)
Donna Griebel, MD, Division Director
Ruyi He, MD, Team Lead
Karen Berry, MD, Medical Officer

Proposed New Drug: Dronabinol oral solution

NDA/IND: 205525/075228

Sponsor: Insys Therapeutics Inc.

Proposed indication: 1) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments
2) Anorexia associated with weight loss in patients with AIDs

Referenced Drug: Marinol® Dronabinol capsules USP (NDA 018651)

Materials Reviewed:

- Sponsor's Initial Pediatric Study Plan dated November 03, 2014
- Sponsor's Meeting Package provided by the DGIEP Project Manager, Mary H. Chung (Refer to Type A Meeting Preliminary Comments for IND 075228)
- Sponsor's Revised Pediatric Study Plans dated January 30, 2015; February 18, 2015; April 8, 2015; and April 17; 2015;

- Labeling for Marinol available on Drugs@FDA under NDA 018651
- Consult review by Dr. Yodit Belew dated January 21, 2015
- Sponsor's Response to Information Requests available in DAARTs and emails provided by DGIEP project manager(s)
- Pediatric Review Committee (PeRC) documents and final meeting minutes. (Refer to DAARTs PeRC Minutes drafted by Dr. Jane E. Inglese dated January 28, 2015)

Consult Request Date: November 24, 2014

Consult Question: DGIEP requests DPMH Pediatric Team's assistance with:
- Responding to the sponsor's Type A meeting request discussion questions (internal pre-meeting and sponsor meeting participation requested)
- Review of the iPSP

Overview of Medical Marijuana Development and Usage in Pediatric Patients

The sponsor proposes to develop an oral solution form of dronabinol, a synthetic marijuana product. On October 10, 2014, DGIEP in consultation with DPMH, refused to file the original New Drug Application submitted August 12, 2014, because the application lacked a pediatric study plan. The sponsor subsequently requested a Type A Meeting on November 3, 2014, and submitted their initial Pediatric Study Plan on November 6, 2014, for Agency review and concurrence. The sponsor plans to seek approval of their product under the 505(b)(2) pathway, using Marinol capsules (approved May 31, 1985, under NDA 018651) as the referenced drug. Notably, Marinol is the only marijuana-based prescription medicine currently available in the United States. Another synthetic cannabinoid, nabilone (Cesamet), has been approved for use in the United States and United Kingdom for chemotherapy induced nausea and vomiting (CINV). (b) (4) The NIH funds collaborative programs to promote the commercial development of drugs for conditions such as AIDS, cancer, glaucoma, multiple sclerosis, chronic pain, addiction, spinal cord injuries and epilepsy…such programs supported most of the research that originally brought dronabinol to the market.[1] (b) (4)

Researchers at the Institute of Medicine conducted and published a critical review of the scientific literature pertaining to the use of medical marijuana and its chemical components. In the final report entitled "Marijuana and Medicine: Assessing the Science Base," the group evaluated the effects of chronic marijuana use on physical and mental health; compared the effectiveness of using marijuana versus approved medications to treat specific disorders; and examined the role of marijuana as a gateway drug to other illicit drug use.[2] Medical marijuana use is currently legal in 23 U.S. states.[3] Science is only one facet of the medical marijuana controversy.[2,Error! Bookmark not defined.,Error! Bookmark not defined.] Meaningful application of currently existing knowledge regarding the medical use of marijuana is obscured by conflicting federal and state legislative requirements.[3,2,Error! Bookmark not defined.,Error! Bookmark not defined.] Furthermore, there are conflicting published data from studies documenting the physical and psychological effects of "acute" and "chronic" medical marijuana usage.[8,9,10] In the opinion of this reviewer, to render an "educated" opinion/review without also considering the broader "context of use" would be both irresponsible and unwise. Nevertheless, placing the "objective science" of "medical marijuana usage" into a broader social context is difficult, complex, and beyond the scope of this limited review.

APPEARS THIS WAY ON ORIGINAL

One of the predominantly unresolved issues remains, "Does public perception of the benefits of medical marijuana lead to increased abuse and/or illicit usage?" Some have argued that medical marijuana legalization will increase rates of adolescent marijuana use and increases health-related risks, particularly among adolescents.[2,4] Similarly, some experts posit that public acceptance of the possible medicinal value of marijuana will undermine the drug's reputation as a "dangerous drug" among young people.[3] Changes in marijuana use data suggest that legalization of the drug does indeed impact adolescent "intent to use".[5] A study by Friese and Grube concluded that legalizing marijuana use was linked to an increase in adolescent marijuana use by up to 30%.[4] There are additional data gathered between 1978 and 2006 which suggest that a declining proportion of adolescents perceive any harmful risks associated with regular marijuana usage.[6] Levels of recreational marijuana usage and dependence appear to be more common in states with laws that legalize medical marijuana use.[7] However, additional data are needed to

support or refute the assertion that legalizing marijuana would prompt increased drug abuse among those who are medical marijuana users (the actual population for which the drug is being developed). This nuance is important. However, one can only speculate the answer to any of these questions at this time based on reasonable inference from past usage of other prescription medications with similar abuse potential. Furthermore, none of the existing studies have consistently and clearly quantified and defined the frequency and duration of medical marijuana usage which poses harm as opposed to "minimal risk over benefit". Consequently, additional data are needed to support or refute the assertion that legalizing marijuana would prompt increased drug abuse among those who are medical marijuana users in addition to increased illicit drug use. What is known about marijuana use in adolescents? Changes in marijuana use rates are consistent with data suggesting that adolescents' intent to initiate marijuana use would increase if the product were legalized for medical purposes.[8] However, this reviewer could not find any existing study that directly addresses if legalization of medical marijuana resulted in an actual increase in the nonmedical usage of marijuana and/or increased drug abuse among medical users. "The linkage between adolescent marijuana use and the legal status of medical marijuana persists even though state laws legalizing medical marijuana typically restrict use by those under the age of 18 years."[1] Ultimately, the issues and discussions regarding the legalization of medical marijuana will likely be akin to those generated prior to the legalization of alcohol and tobacco products.

While public opinion may change regarding the "social acceptability" of medical marijuana usage, there remains a significant body of scientific evidence suggesting that repeated use of marijuana during adolescence can produce long-lasting cognitive impairments and increases the risks of serious mental illness.[1] Studies are lacking that clearly define the relationship between adolescent medical marijuana usage and abuse potential/clinical outcomes. Furthermore, analyses of data generated from drug development programs for the use of medical marijuana in pediatric patients are likely to be influenced by individual and environmental covariates.[9] Because history has provided us with very little evidence that regulators can effectively prohibit access to recreational marijuana while simultaneously increasing the availability of medical marijuana, asking for additional data to assess the safety and effectiveness of prescription dronabinol in adolescents in a more "controlled" pre-marketing setting may provide useful data and insight that will ultimately benefit the public health and protect vulnerable pediatric populations. Furthermore, there are no data available concerning the pharmacodynamics properties of Dronabinol usage in younger patients. (See below.)

Background History for Dronabinol and Related Compounds

On August 12, 2014, Insys Therapeutics, Inc. (Insys) submitted a 505(b)(2) new drug application for a new formulation of dronabinol. The applicant's product, a new formulation dronabinol intended for oral delivery, contains synthetic delta-9-tetrahydrocannabinol (also referred to as delta-9-THC or THC). The drug product acts on cannabinoid CB_1 and CB_2 receptors in the nervous system. [Notably delta-9-THC is also a naturally occurring component of Cannabis sativa L. (marijuana)]. The referenced drug product for this application is the Marinol® oral capsule formulation, approved May 31, 1985, under NDA 18651. According to the labeling for Marinol® (dated June 21, 2006, and available at Drugs@FDA), the drug is approved for the following adult indications:

1) The treatment of AIDS-related anorexia associated with weight loss (AIDs wasting); and
2) The treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to response adequately to conventional anti-emetic treatments. (CINV)

According to the applicant, orally administered cannabinoid compounds have a bioavailability ranging from 5 to 20%. The applicant purports that up to 80% of the administered dose of the referenced drug product is lost due to inefficient absorption or destruction in the liver. Consequently, a wide range of oral doses of existing cannabinoid products are needed to produce effects on the central nervous system. Additionally, onset of "peak drug effects" occurs several hours after drug administration. Because of the varying bioavailability "issues" associated with use of existing cannabinoid compounds, the sponsor believes there is a medical need for their product, which is designed to deliver a more consistent dosage and therapeutic effect.

Reviewer Comment: Marinol is the only marijuana-based prescription medicine currently available in the United States. Another synthetic cannabinoid, nabilone (Cesamet), has been approved for use in the U.S. and United Kingdom for Chemotherapy Induced Nausea and Vomiting (CINV). Dronabinol, the "synthetic" THC in the

approved Marinol product, is identical to the naturally occurring THC in the marijuana plant. (Notably marijuana contains over 60 different cannabinoids comprising a dozen distinct cannabinoid-types. The delta-9-THC component is the primary psychoactive constituent and the structurally related cannabidiol (CBD) component may oppose the cognitive impairment produced by acute exposure to delta-9-THC. Consumption of unprocessed plant material for medical purposes is complicated by inconsistent drug composition, content and effects.

Cannabinoids behave differently in the human body depending on whether they are inhaled, injected, or swallowed.[2,3] A variety of factors influence the use and potential misuse/abuse of psychoactive drugs. Factors consistently documented to correlate with psychoactive prescription drug abuse include older age, poor physical health, and female gender.[10] The more rapidly a drug takes effect, the more likely the drug product will be abused.[10] Research suggests that CB1 and CB2 receptors adapt to chronic THC exposure in ways that contribute to tolerance. "Most studies on brain cells detected a decrease in the production of cannabinoid receptors under conditions that mimicked prolonged exposure to cannabinoids."[2] Tolerance may develop at different rates in different regions of the brain, which may explain why tolerance to some effects develops more quickly than other effects.[11]

Labeling for the referenced drug, Marinol, contains the following "pediatric-related" language:

- MARINOL Capsules is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing MARINOL Capsules for children because of the psychoactive effects."
- MARINOL Capsules should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these patient populations.
- Use of MARINOL Capsules is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.
- The pharmacokinetic profile of Marinol capsules has not been investigated in pediatrics.

Labeling contains the following specific information under "Drug Abuse and Dependence":

> "MARINOL Capsules is one of the psychoactive compounds present in cannabis, and is abusable and controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration. Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgment, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of MARINOL Capsules for therapeutic purposes. In an open-label study in patients with AIDS who received MARINOL Capsules for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse. An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include "hot flashes", sweating, rhinorrhea, loose stools, hiccoughs and anorexia. These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol."

Reviewer Comment: This reviewer notes that there are no definitions provided for "prolonged high dose administration" and "chronic abuse" as they appear above in the excerpts reproduced from the "Drug Abuse and Dependence" section of the currently approved Marinol labeling. This reviewer searched the medical literature to find a "standardized" definition of "chronic" and "chronic disease". The literature does not support a single

uniform definition of "chronic" or "chronic disease", however recurrent themes for chronic disease include the following:

- *"non-self-limited nature,*
- *the association with persistent and recurring health problems,*
- *duration measured in months and years, not days and weeks."*[11]

Although use of dronabinol for AIDS wasting will likely be "chronic" in nature, usage of the drug for CINV could possibly be considered "short-term" or "episodic" (depending on the etiology and natural history of the underlying cancer for which the chemotherapy is prescribed). According to one source, in 2001, 80% of adult patients on Marinol were using the drug to relieve the symptoms of AIDS wasting, 10% were using the product to relieve the symptoms of CINV, and the remaining proportion for off-label conditions.[3]

Regulatory History and Prior Discussions for the Initial Pediatric Study Plan (iPSP)

In August of 2014, a New Drug Application (NDA 205525), was submitted to the Division of Gastroenterology and Inborn Error Products (DGIEP). Following DGIEP and DPMH collaborative review of the initial NDA submission, in October of 2014, the Division issued a "refuse-to-file" (RTF) letter to the applicant citing that the application did not contain a materially complete and agreed upon initial Pediatric Study Plan (iPSP). (Refer to DAARTs document Reference ID 3642727). DGIEP advised the applicant to submit their initial Pediatric Study Plan (iPSP) to the IND. (Refer to DAARTS document Reference ID 3651099.)

On November 03, 2014, the sponsor submitted an iPSP to IND 075228 for dronabinol, which requested (b) (4) to submit the PREA required assessments in pediatric patients ages 0 to 17 years of age with Chemotherapy Induced Nausea and Vomiting (CINV). This initial iPSP submission did not address the other indication in the labeling for the referenced drug product (i.e. anorexia associated with weight loss in patients with AIDS). Along with the iPSP submission, the applicant also submitted a Type A meeting request to discuss the adequacy of their submission for addressing issues in the RTF correspondence. DGIEP and DPMH met with the sponsor on December 4, 2014. In the formal meeting minutes, the sponsor was asked to provide all available use data for both on-label and off-label uses of the reference product in all relevant pediatric age groups to support their plans to (b) (4) studies required under PREA. Additional general comments related to the PREA requirements were provided. (Refer to DAARTs document with Reference ID 3666795.)

The sponsor resubmitted their iPSP on February 18, 2015. This submission contained a request for a complete waiver to study pediatric patients with AIDS associated anorexia and weight loss. The sponsor asserted that necessary studies were highly impractical due to the small number of patients and provided data from the Centers for Disease Control to support their position. The sponsor also requested (b) (4) to study pediatric patients (b) (4) suffering from chemotherapy inducted nausea and vomiting and failure to respond adequately to conventional antiemetic treatments. In the second "resubmission", the sponsor maintained that "safer approaches" (relative to the proposed dronabinol) were available to treat pediatric patients with (b) (4) AIDS wasting. Interestingly, the sponsor also stated that there were several possible off-label uses for their proposed dronabinol product including possible usage in pain syndromes, spasticity due to various causes, trichotillomania, and the tics of Tourette's syndrome. Despite the potential for "off-label" usage the sponsor argued that dronabinol oral solution was unlikely to be the cannabinoid of choice because of unreliable bioavailability; the existence of other preparations; and the increased risk of psychiatric side effects associated with cannabis use rendering the drug unsafe for usage in pediatric patients.

Reviewer Comment:
The applicant stated that their proposed product is designed to be more consistently bioavailable. This directly conflicts with their aforementioned argument.

There was no agreement on the sponsor's revised pediatric development program. (b) (4) . Futhermore the alcohol content of the drug product was below limits permitted by the FDA and therefore

FDA disagreed with the sponsor's argument that the alcohol content posed a safety concern that precluded the study of pediatric patients.

The iPSP was discussed by the Pediatric Review Committee (PeRC) on January 28, 2015. (Refer to PeRC Meeting Minutes Reference ID 3699286.) PeRC did not agree with the applicant's resubmission. Thus, DGIEP sent, another formal advice letter to the sponsor on January 30, 2015. (Refer to DAARTs Reference ID 3694659.) The sponsor was advised that in order to fulfill the PREA requirements, they would need to:

- Address both indications in all pediatric age groups for the currently approved labeling for the referenced product, Marinol.
- Clarify their rationale for waiver and deferral requests and supply supporting data to support their requests.
- Describe any plans to develop an age-appropriate pediatric formulation(s).
- Provide pharmacokinetic data from studies with the pediatric dronabinol formulation because of "the unreliable bioavailability nature of the drug".
- Perform additional juvenile animal toxicity studies to support the safety of the pediatric drug development program prior to the initiation of clinical trials in children.

On February 18, 2015, the applicant resubmitted their response along with another revision of the iPSP. In the February submission, the sponsor proposed to (b) (4)

(b) (4)

Reviewer Comment: The Division's request to study CINV for all pediatric age groups is similar to (and consistent with) the PREA requirements for other products seeking an indication for (b) (4) *CINV. Pathways for chemotherapy-induced emesis are more understood than those for nausea. Previously, researchers focused on prevention of CINV as a primary measure of treatment efficacy. Although serotonin (5-HT_3) receptor antagonists and neurokinin-1 inhibitors have reduced the rates of acute vomiting associated with cancer chemotherapy, there are patients who still experience acute vomiting, delayed and/or breakthrough chemotherapy-induced nausea and vomiting and reduced efficacy in the prevention of nausea.[12] During prior discussions, the PERC agreed that there may be an unmet medical need for those patients who experience breakthrough or delayed CINV. There are limitations in the existing body of clinical research literature that supports the use of cannabinoids for CINV. Most studies of cannabinoid use for CINV were conducted in a setting where the drug was used prophylactically rather than for treatment or rescue therapy and therefore scientific data supporting cannabis use in treatment of CINV are of marginal value.[8] Additional challenges that limit proper conclusions regarding use of this drug product in this patient population include deficient study methodologies, failure to stratify results according to the chemotherapeutic agent used, and failure to delineate acute and delayed symptoms.*

An international professional panel developed guidelines for approaching the prevention and anticipatory treatment of CINV in children based on systematic literature reviews.[13] Gaps in the evidence used to support the recommendations were also identified. According to one article, the current standard of care with respect to the prevention of acute CINV in children includes the administration of a 5-HT3 antagonist with or without a

corticosteroid, depending on the emetogenicity of the chemotherapy given. However, there are a number of products used for the prevention and treatment of CINV. "Appropriate selection of antiemetic agents for children receiving chemotherapy is limited by the lack of rigorous evidence to support one regimen over the other."[14] There are a lack of data to guide the treatment of breakthrough chemotherapy induced nausea and vomiting, despite initial prophylaxis.[9] Some argue that CINV is a "conditioned response and that optimization of acute and delayed CINV control may help to minimize exposure to the negative stimuli which are required for conditioning to occur.[14] The same authors suggest usage of lorazepam once at bedtime before chemotherapy and once the next day prior to administration of chemotherapy in order to prevent or treat anticipatory CINV in children.[14] Similarly authors argued that "the inconsistent approach to measurement of anticipatory CINV… and the use of unvalidated instruments preclude comparison of results across studies.[14] Furthermore, most of the pharmalogical interventions evaluated for treatment of anticipatory CINV are benzodiazepines.[14]

The sponsor's proposed product supposedly provides greater flexibility of use, ease of dose titration, and more predictable exposure which may better meet the needs of patients who require weight-based dosing. If the sponsor's assertion is true, there may be a possible therapeutic benefit for use of this product in pediatric patients. In 2004, the American Academy of Pediatrics Committee on Substance Abuse and Committee on Adolescence provided a policy statement supporting rigorous scientific research regarding the use of cannabinoids for the relief of symptoms not currently ameliorated by existing legal drug formulations.[15] This policy was updated online January 26, 2015, and in a technical report appearing in Pediatrics in March 2015. The AAP maintains that, "Only limited research has been conducted on medical marijuana for adults, and there have been no published studies of cannabinoids -- either in the form of marijuana or other preparations -- that involve children. The Academy supports further study of cannabinoids, which limited research to date shows can help specific conditions in adults"[16]. As stated previously in the introduction, the legalization of medical marijuana may potentially increase recreational usage of the drug and the lack of published studies of cannabinoid usage in pediatric populations supports the argument for further rigorous study of the safety and effectiveness of marijuana preparations.

In the February 2015 submission, the sponsor requested a full waiver to study all pediatric AIDS patients with anorexia associated with weight loss on the grounds that necessary studies were highly impracticable. The sponsor maintained that only 300 pediatric patients per year develop AIDS and provided CDC Data to support their request. They argued that while short-term weight gain was demonstrated with cannabinoid use in HIV-infected patients, most weight gains were in fat mass and serious adverse events were reported from adult studies. The sponsor presented data from the literature suggesting there was an absence of data to support the assertion that cannabinoids provide improvements in objective outcomes (weight, lean body mass, and energy intake) in patients with HIV-associated wasting. According to the sponsor, a literature search in PubMed using the terms "dronabinol", "HIV infection" and "child" yielded no results.

Reviewer Comment: The reader should refer to the review of Dr. Yodit Belew, consultant from the Division of Antiviral Products. Dr. Belew stated in her review that there is no standardized approach to select medications used for appetite stimulation patients with AIDS. Dr. Belew also stated that dronabinol has not been shown to increase total weight despite modest increases in appetite. She then concluded that the incidence and prevalence and pediatric AIDS cases in the US is very low and given the CNS side effects there was likely little or no use/need for dronabinol use in the pediatric AIDS population. (DAARTs Reference ID: 3690077)

In their PSP the sponsor presented incidence and prevalence data for patients with both HIV and AIDS. The referenced product, Marinol, is approved for use in patients with AIDs wasting. The CDC defines AIDS wasting syndrome as the involuntary loss of more than 10 percent of body weight, accompanied by diarrhea or fever that last more than 30 days and is not attributable to another illness. Wasting occurs secondary to cachexia combined with starvation. The underlying processes that cause cachexia are similar in for the final stages of cancer and AIDs. While starvation simply requires one to increase consumption, controlling cachexia requires controlling the disease that triggered the process and artificially stimulated the body's metabolism. Although language in the labeling for Marinol relates to drug usage in AIDS wasting, off-label usage in HIV patients is plausible. There are data to suggest that patients affected with HIV begin losing muscle and lean tissue mass before developing full-blown AIDS.

The data presented by the sponsor were unclear and did not appear consistent with the indications in the approved labeling of the referenced drug. Case-definitions for HIV infection and AIDs have been modified and therefore, the CDC data (presented by the sponsor to support their position) may underestimate a true disease prevalence and incidence. According to the CDC, the term "diagnosis of HIV infection" refers to a diagnosis of HIV infection regardless of the person's stage of disease (stage 1, 2, 3{AIDS} or unknown) at the time of diagnosis and does not necessarily reflect when the person became infected.[17] More importantly diagnosis of HIV infection does not represent a true incidence (new infections over a predefined time period) because not all infected persons have been tested or tested at a time when their infection could be detected and diagnosed.[11]

Methods used to determine the number of Stage 3 AIDs cases at the time of HIV diagnosis have been modified over time. According to an article published in Morbidity and Mortality Weekly, "For adults and adolescents (i.e., persons aged >13 years), the human immunodeficiency virus (HIV) infection classification system and the surveillance case definitions for HIV infection and acquired immunodeficiency syndrome (AIDS) have been revised and combined into a single case definition for HIV infection (1–3). In addition, the HIV infection case definition for children aged <13 years and the AIDS case definition for children aged 18 months to <13 years have been revised. No changes have been made to the HIV infection classification system, the 24 AIDS-defining conditions for children aged <13 years, or the AIDS case definition for children aged <18 months."[18]
Consequently, the CDC data may not provide the entire scope of pediatric HIV cases.

Persons infected with HIV are being diagnosed at earlier stages and at younger ages. These patients are living longer. However reporting delays (the time between diagnosis or death and the reporting of diagnosis or death to the CDC) persist and may differ among demographic and geographic categories. Although improved HIV therapies have markedly improved survival rates, for the patient who does progress to develop an AIDs associated wasting syndrome, the risk of using a product like dronabinol (or one of its constituent components) may outweigh the benefits. From 2009 through 2012, the estimated number of persons in the United States living with diagnosed HIV infection increased.[19] By the end of 2012 an estimated 914, 826 people were living with a diagnosis of HIV infection.[19] In 2013, approximately 187 children per year under 13 years of age were diagnosed with HIV infection in the United States.[20] Approximately 1,900 people ages 13 to 19 years were diagnosed with HIV infection in 2013.[19] By the end of 2013, 9400 pediatic patients less than 13 years of age were estimated to have a diagnosis of Stage 3 AIDS. Approximately 10,000 patients ages 13 – 19 years in the US had a diagnosis of Stage 3 AIDS. Overall between 1992 and 2013, the number of children ages 13 years and younger who were diagnosed with Stage 3 AIDS has been steadily decreasing. In the U.S., the rate of HIV transmission has declined by 89% since the peak of the epidemic.

Based on available epidemiological data, the sponsor should qualify for a partial waiver to study anorexia associated with AIDs wasting in pediatric patients less than 13 years of age on the grounds that studies are highly impracticable. However a trial in older adolescents (at least 14 years and above) may be feasible and the sponsor will likely have to submit PK and some additional efficacy data. At the end of 2011, an estimated 1,201,100 persons aged 13 years and older were living with HIV infection in the United States. It is believed that approximately 160,300 (14%) of the estimated number were living infections had not been diagnosed. At the end of 2012, there were an estimated 914,826 persons living with diagnosed HIV infection in the United States.[17,20,21] HIV prevalence data between the years 2006 – 2010 reveal that approximately 56,000 patients ages 13 – 24 years were living with HIV.[17,20] To reiterate, there are delays in reporting the prevalence data that also factor into decisions regarding deferrals and waivers.

The sponsor was advised of the need to present an additional justification (b) (4) and other recommendations for the iPSP during a teleconference held on March 26, 2015. Additional comments to the sponsor were provided on April 3, 2015. Following additional guidance from DGIEP and DPMH, the sponsor submitted their response to information requests and a revised iPSP dated April 9, 2015. The final revised iPSP is summarized below.

Overview of Dronabinol Pediatric Product Development and Specific Waiver/ Deferral Requests

The sponsor is not planning to [redacted (b) (4)]. The sponsor will complete nonclinical juvenile animal studies and seek FDA approval prior to commencing clinical studies in pediatrics. Proposed clinical studies for each indication are:

1) Indication: Treatment of anorexia associated with weight loss in patients with AIDS (AIDS wasting):
   The sponsor appears to request a partial waiver to study pediatric patients ages 0 to 14 years because necessary studies are highly impracticable because the patient population to be studies is small and geographically dispersed. The sponsor requests a deferral to conduct a [redacted (b) (4)] trial in pediatric AIDS patients ages 15 to 17 years old. The objective of the study will be to [redacted (b) (4)].

Reviewer Comment: Sections of the proposed pediatric plan are inconsistent. Specifically in one section the sponsor appears to be requesting a partial waiver to study pediatric patients ages 0 to 12 years of age for this AIDS wasting indication. The sponsor will need to revise the plan so that the age "cut-offs" are consistent throughout the document.

2) Indication: Treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional anti-emetic treatments (CINV):
   The sponsor appears to be planning to conduct a [redacted (b) (4)] trial in pediatric cancer patients to facilitate [redacted (b) (4)] tolerability and efficacy trial in pediatric patients ages 0 to 17 years.

   Reviewer Comment: The sponsor will need to update the final iPSP to be consistent throughout the document. DGIEP currently does not [redacted (b) (4)]

OVERVIEW OF THE DISEASE(S)

a. **Anorexia associated with weight loss in patients with AIDS (AIDS wasting)**

Weight loss associated with anorexia is only one of the causes of HIV-associated wasting syndromes. Other causes include malabsorption, diarrhea, opportunistic infections, and altered metabolic states. [21] According to the sponsor, excessive cytokine production may also alter muscle protein metabolism, decreasing transcription factors essential for skeletal myoblast differentiation and activating the ubiquitin-proteasome system to accelerate protein degradation. Elevated resting energy expenditures are also associated with HAART therapy and may be mediated through activation of the sympathetic nervous system or through an increase metabolic demand associated with restoration of immunity. Disruptions in growth hormones and insulin-like growth factor 1 may contribute to the AIDs wasting syndrome. There are no published data comparing the underlying pathophysiology of AIDS/HIV associated wasting syndromes in adult and pediatric patients. Treatment options for use in anorexia-associated with weight loss in AIDs patients include marinol, nablixone, and megestrol acetate. However, all have limited efficacy and issue with intolerable adverse effects.

b. **Nausea and vomiting associated with cancer chemotherapy in patients who failed to response adequately to conventional anti-emetic treatments. (CINV):** The vomiting center is the primary structure that modulates nausea and vomiting. Individual differences in response to emetogenic stimuli may potentially be explained by varying degrees of stimulation required to stimulate the vomiting center to reach the threshold of nausea and vomiting.[22] The chemoreceptor trigger zone was identified in the 1950s and is responsible for emetogenic potential of chemical agents.[23] The three main neurotransmitters involved in the neuroanatomy and neurochemistry of CINV and postoperative nausea and vomiting are 5-HT, Substance P (SP), and dopamine. [23]There are no published studies specifically addressing the pathophysiology of CINV in children. There are no pediatric products approved for use in the treatment of chemotherapy induced nausea and vomiting. However, there have been a number of clinical studies demonstrating the benefit in decreasing chemotherapy induced nausea and vomiting using pharmacologic agents including phenothiazines, benzamide derivatives, corticosteroids, cannabinoids, and butyrophenones.[24] The current standard of care with respect to the prevention of acute CINV in children includes the administration of a 5-HT3 antagonist with or without a corticosteroid, depending on the emetogenicity of the chemotherapy given. Appropriate selection of antiemetic agents for children receiving chemotherapy is limited by the lack of rigorous evidence to support one regimen over the other and there are a lack of data to guide the treatment of breakthrough chemotherapy induced nausea and vomiting, despite initial prophylaxis.[11,12]

2) OVERVIEW OF THE DRUG PRODUCT

The sponsor's new formulation is a dronabinol oral solution containing the same active ingredient as the referenced drug, Marinol. Currently available formulations of dronabinol have a greasy consistency that presents manufacturing problems. The drug product is difficult and expensive to purify and does not readily dissolve in water. The bioavailability of the product is unpredictable resulting in a large degree of inter-patient drug concentration variability. Furthermore, only a fraction of the ingested compound reaches the patients circulation, the peak onset of action is delayed (2 to 4 hours after ingestion), and the product has a number of adverse side effects.

3) [redacted] (b) (4)

Reviewer comment: DPMH agrees that the sponsor's plan for [redacted] (b) (4) *is acceptable.*

4) REQUEST FOR DRUG- SPECIFIC WAIVER(S)

a. Indication: Treatment of anorexia associated with weight loss in patients with AIDS (AIDS wasting):
The sponsor is requesting a partial waiver to study pediatric patients ages 0 to 12 years because necessary studies are highly impracticable because the patient population to be studied is small and geographically dispersed. The sponsor also maintains that studies are highly impracticable in the patient population from 0 to 14 years of ages. To support their request the sponsor submitted data from the CDC report entitled "Diagnoses of HIV Infection in the United States and Dependent Areas 2009 - 2013" published in 2015. According to the sponsor, "From 2009 through 2013, the number of diagnoses of HIV infection among children less than 13 years of age ranged between 232 – 164 patients per year. During the same time span, the number of children less than 13 years of age who went on to develop AIDS ranged from a high of 23 children in 2010 to a low of 7 children in 2013. Cumulative in 2013, there were approximately 9,399 pediatric patients under the age of 13 years of age who had AIDS. Approximately 752 patients would likely develop anorexia assuming an 8% occurrence rate. The sponsor maintains that data indicate that for the age ranges from 0-12, it would be impossible or impracticable to conduct a study to conduct a study in this age range due to the low number of patients in the United States.

Reviewer Comment: The grounds for the sponsor's assumption that 8% of pediatric paients with HIV will develop anorexia is not entirely clear. However, DPMH believes that the sponsor request for a partial waiver to study pediatric patients less than 13 years of age for this indication is reasonable. The sponsor presents conflicting information and will need to clarify if they are requesting a waiver to study pediatric patients less than 14 years of age (inclusive) or ages 0 to 12 years of age. According to the CDC data presented by the sponsor, a waiver in pediatric patients less than 13 years of age is easily justifiable and as stated previously in this review acquiring additional safety and efficacy data for use of this preparation in adolescents seems both warranted and prudent because of previously existing bioavailability issues and the drug's abuse potential.

(b) (4)

[redacted]

Table 1 Summary of Planned Nonclinical Studies and Clinical Pediatric Studies for Dronabinol Oral Solution.

PLANNED NONCLINICAL STUDIES			
Species	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
Rats	Juvenile Tox	To support initiation of studies in children 0-17	N
PLANNED PEDIATRIC CLINICAL STUDIES			
Age Group	**Type of Study**	**Comments**	**Deferral Request Planned for the Study (Y/N)**
(b) (4)			

(b) (4)

Source: page 22 of 35 Sponsor's submission dated April 08, 2015.

NON-CLINICAL STUDIES

The sponsor plans to begin the nonclinical study program following Agency concurrence with the proposed pediatric study plan. Prior to the conduct of any clinical trial, the sponsor will conduct a juvenile toxicology study and based on those results commence with the first PK trial in pediatric patients.

The sponsor plans to conduct a 28 day, daily, repeat-dose, oral gavage dose-range finding study to select appropriate doses that will then be used in a 3-month repeat dose chronic juvenile rat toxicity study of Delta-9-THC, followed by a 28-day recovery period. Draft protocols were submitted for nonclinical review by April 1, 2015. If the juvenile toxicology study starts in 2015, the pediatric data requested will be available in 2017. The sponsor commits to not initiating any clinical trials in pediatric prior to submission and review of the final juvenile rat study reports to the Agency.

Reviewer Comment: DPMH defers the acceptability of the juvenile pharm-tox studies to the nonclinical reviewer. The nonclinical program will need to support the study of dronabinol across the entire pediatric age range that will be studied. The proposed staggered approach seems appropriate given the lack of available data for use of this

product in pediatric patients and the known risks associated with cannabinoid usage. DPMH defers additional comments to the nonclinical reviewers.

(b) (4)

Reviewer comment: DPMH agrees that the sponsor's plan is acceptable. DPMH defers additional comments to the Division CMC reviewer

9. CLINICAL STUDIES

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: *DPMH recommends that the protocol and SAP be submitted for agreement before pediatric studies are initiated. The sequential approach is reasonable.*

10. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN

The sponsor plans to submit the required pediatric data by July 2020. Details regarding the nonclinical and clinical pediatric timelines are provided:

Nonclinical studies

• 28-day, daily, repeat-dose, oral gavage dose-range finding study to determine doses in 3-month repeat dose juvenile toxicity study (protocol submitted)

- o Estimated study initiation date: no later than Aug 2015
- o Estimated final report submission date: no later than December 2015

• Three-month repeat dose toxicity and toxicokinetic study in juvenile rats with a 28-day recovery period

- o Estimated protocol submission date: no later than December 2015
- o Estimated study initiation date: no later than March 2016
- o Estimate final report submission date: no later than January 2017

Clinical Studies

• PK studies

- o Estimated protocol submission date: no later than May 2017
- o Estimated study initiation date: no later than July 2017
- o Estimated final report submission date: no later than December 2017

• Efficacy/safety studies

- o Estimated protocol submission date: no later than January 2018
- o Estimated study initiation date: no later than March 2018
- o Estimated final report submission date: no later than July 2020

• Target date of application submission

- o No later than January 2021

Reviewer Comment: The timing of the studies should not be tied to product approval and therefore the sponsor's approach appears acceptable.

PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES

The sponsor plans to request a deferral of clinical studies until the nonclinical program is completed. In the final submission, the sponsor requests a deferral to begin the [redacted] trial in CINV pediatric patients until three months after the juvenile toxicology study is complete. Results of the juvenile toxicology study will be submitted to FDA for review prior to the onset of clinical studies. The sponsor also plans to request a deferral for the [redacted] tolerability and efficacy studies until the [redacted] trial in CINV pediatric patients is complete.

Reviewer Comment: PMHS defers to the nonclinical reviewer to comment on whether full review of data from the juvenile toxicology study are required before initiating trials in adolescents. However, initiation of the juvenile toxicology study need not be delayed and protocols should be submitted as soon as possible for Agency concurrence. DPMH agrees that the sponsor's proposed staggered approach is reasonable. The sponsor should be reminded that final decisions regarding requests and waivers are generated at the time of NDA approval.

Conclusions

DPMH and DGIEP participated jointly in discussions with the sponsor. DPMH recommended agreement with the sponsor's pediatric study plan submitted April, 2015, provided that modifications were made to ensure consistency throughout the document. The sponsor agreed to clarify age cut-offs for proposed partial waivers and deferral requests throughout their document.

Summary

Insys Therapeutics, Inc. (Insys) is developing a new formulation of dronabinol, an oral solution containing synthetic delta-9-tetrahydrocannabinol (also referred to as delta-9-THC or THC) for use in the treatment of :

1) Anorexia associated with weight loss in patients with AIDS (AIDS wasting); and
2) Nausea and vomiting associated with cancer chemotherapy in patients who failed to response adequately to conventional anti-emetic treatments. (CINV)

The sponsor plans to submit a 505(b)(2) new drug application using Marinol (a synthetic THC product approved in 1985) as the referenced drug. Marinol is the only marijuana-based prescription medicine currently available in the United States. Dronabinol, the "synthetic" THC in Marinol is identical in every way to the naturally occurring THC in the marijuana plant. The THC component of the proposed drug product is the primary psychoactive constituent. The structurally related cannabidiol (CBD) component may oppose cognitive impairment produced by acute exposure to delta-9-THC. Using unprocessed plant material for medical purposes is complicated by inconsistent drug composition, content and effects. There are bioavailability "issues" associated with use of existing Dronabinol preparations, therefore the sponsor believes there is a medical need for their product.

The issues and discussions regarding the legalization of marijuana are likely to be akin to those generated prior to the legalization of alcohol and tobacco products. Full discussion of the social acceptability and consequences of legalized marijuana are beyond the scope of this review. There are data to suggest that marijuana legalization will lead to increases in recreational and medical usage. Study design restrict cross comparisons of clinical outcomes. Because history has provided us with very little evidence that regulators can effectively prohibit access to recreational marijuana while simultaneously increasing the availability of medical marijuana, asking for additional data to assess the safety and effectiveness of prescription dronabinol in adolescents in the pre-marketing setting may provide useful data and insight that will benefit the public health.

Summaries of the sponsor's proposed clinical pediatric plan are outlined below (by indication):

Indication: "Treatment of anorexia associated with weight loss in patients with AIDS (AIDS wasting)"
Insys is requesting a partial waiver to study pediatric patients ages 0 to 14 years because necessary studies are highly impracticable because the patient population to be studies is small and geographically dispersed. DPMH believes that a request for a partial waiver to study pediatric patients less than 13 years of age for this indication is reasonable. According to the CDC data presented by the sponsor, a waiver in pediatric patients less than 13 years of age is easily justifiable and as stated previously in this review acquiring additional safety and efficacy data for use of this preparation in adolescents seems both warranted and prudent because of previously existing bioavailability issues and the drug's abuse potential. The sponsor will need to edit their proposed iPSP for consistency throughout the document.

Indication: "Treatment of nausea and vomiting associated with cancer chemotherapy in patients who failed to adequately respond to conventional anti-emetic treatments (CINV)" Insys requests (b) (4)

[redacted] (b) (4) Additionally, the sponsor will need to update the final iPSP to be consistent throughout the document and to reflect that they have agreed to conduct nonclinical juvenile animal studies and PK, safety, and tolerability studies in pediatric patients with CINV who are ages 0 to 17 years of age. DGIEP currently [redacted] (b) (4) . There may be an unmet need for use of the product in pediatric patients with breakthrough or delayed CINV despite prophylactic antiemetic usage.

DPMH attended internal and sponsor meetings with DGIEP occurring between November 2014 and May 2015 to discuss the initial Pediatric Study Plan (PSP) and subsequent revisions. DPMH provided recommendations for the Division's consideration during these meeting. Additionally DPMH actively participated in sponsor interactions and attended two presentations for review of the iPSP by the PeRC Committee. The last review of the iPSP occurred on May 13, 2015 and the reader should refer to meeting minutes for additional comments. Additionally the reader is directed to the final agreement letter generated by the Division for the iPSP on May 19, 2015, and housed in the DAARTs application. (Refer to DAARTs document under IND 075228).

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/s/

ERICA WYNN
12/01/2015

LYNNE P YAO
12/03/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Review

Date:	11/24/2015
Reviewer(s):	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader	Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Deputy Director:	David Shih, MD MS Division of Epidemiology I
Drug Name(s):	dronabinol (Marinol)
Subject:	Review of the Literature for the Postmarketing Safety of Dronabinol (Marinol)
Application Type/Number:	NDA 205525
Applicant/sponsor:	Insys Therapeutics, Inc.
OSE RCM #:	2015-1660

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EXECUTIVE SUMMARY

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) draft safety information for dronabinol oral solution (NDA 205525) and to ensure the Prescribing Information reflects information available about dronabinol safety, the Division of Epidemiology I (DEPI) reviewed the postmarketing medical literature for the safety of dronabinol (Marinol).

Dronabinol is Δ^9-tetrahydocannabinol (THC), the main psychoactive compound in marijuana. In 1985, FDA approved Marinol (NDA 018651), an oral THC capsule, for treatment of (1) anorexia and weight loss in AIDS patients and (2) nausea and vomiting from cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. In June 2015, Insys Therapeutics submitted an application for a dronabinol oral solution (NDA 205525). This liquid formulation aims to correct the variable dronabinol pharmacokinetics associated with Marinol.

FDA last reviewed, in 2006, the postmarketing data for dronabinol. To help update the labels for dronabinol-containing products, 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 ($\geq$7 mg/m^2) and systemic hypersensitivity.

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 label as a truthful reflection of the post-2006 medical literature with respect to the safety of dronabinol used for labelled indications.

[1] A companion review from the OSE Division of Pharmacovigilance contains results from a separate evaluation of adverse event case reports.

1. INTRODUCTION

1.1. Background

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) draft safety information for dronabinol oral solution (NDA 205525) and to ensure the Prescribing Information reflects information available about dronabinol safety, the Division of Epidemiology I (DEPI) reviewed the postmarketing medical literature for the safety of dronabinol (Marinol).

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In 2006, the FDA Division of Drug Risk Evaluation (DDRE) in the Office of Drug Safety reviewed May 1985 through February 9, 2006, postmarketing data for dronabinol. The DDRE review evaluated (1) 27 severe adverse event case reports found by search of the Adverse Event Reporting System (AERS) and (2) four published articles found by search of the medical literature. The four articles included (1) one 2001 meta-analysis of 30 randomized controlled studies and (2) reports from three uncontrolled studies. DDRE identified the following two safety matters, since added to the dronabinol label, (1) need for caution in elderly patients and (2) need for caution in patients with a history of seizure.

To help update the labels for dronabinol-containing products, DGIEP asked the Office of Surveillance and Epidemiology (OSE) to review dronabinol adverse event reports and safety information in the medical literature, with special attention to high THC dose ($\geq$7 mg/m^2) and systemic hypersensitivity (OSE RCM #2015-1660). For a verbatim statement of DGIEP's consult request, see Attachment 1. In clarifying correspondence dated July 23 and October 7, DGIEP advised OSE (1) to cover 2006 through present time, the period since the DDRE review and (2) to "limit the scope of the review to (adverse events) that occur with the use of oral dronabinol for the two approved Marinol indications."

In response to DGIEP's consult request, this review contains results from a DEPI evaluation of the medical literature. A companion review from the OSE Division of Pharmacovigilance (DPV) contains results from an evaluation of adverse event case reports.

The Integrated Summary of Safety (ISS), submitted by the sponsor for oral dronabinol solution (NDA 205525), includes results from a search for medical literature published since June 2006. This search found 21 relevant articles that described known adverse gastrointestinal, psychiatric, and nervous system reactions to dronabinol. The ISS did not identify "any new potential safety signals."

Reference ID: 3851948

1.2. Regulatory History

Relevant regulatory events include:

Date	Event
May 31, 1985	Marinol (dronabinol) NDA 018651 approved
June 21, 2006	Label update for MARINOL® (dronabinol) Capsules
June 1, 2015	NDA 205525 submitted for dronabinol oral solution

2. REVIEW METHODS AND MATERIALS

This Review consulted source documents listed in the following table.

Date	Source	Document
March 21, 2006	Office of Drug Safety	Postmarketing Safety Review Drug: Dronabinol (Marinol, NDA# 18-651), All Adverse Events With Serious Outcome
June 14, 2006	OND	Medical Officer Clinical Safety Review
December 27, 2012	OSE	Marinol (dronabinol) and Cesamet (nabilone), Abuse, Misuse, Overdose, Accidents and Deaths
June 1, 2015	Sponsor	Integrated Summary of Safety for Dronabinol Oral Solution, NDA 205525

Figure 1 summarizes DEPI's search for articles published in 2006 or later. Using search terms for dronabinol and an adverse event filter, DEPI identified 1491 records in PubMed or EMBASE. For the search strings used, see Attachment 2: Literature search strategies. DEPI supplemented the PubMed and EMBASE searches with nine records mentioned in other sources, including the Integrated Summary of Safety for NDA 205525 and a meta-analysis commissioned by the Swiss Federal Office of Public Health.[2] The review author (JLW) read the titles and abstracts for the 1354 unique records and retained for full-text review 108 records. To construct the list of 108 articles eligible for full-text review, DEPI sequentially added,

1. The 21 articles cited in the Integrated Summary of Safety for NDA 205525.
2. 24 post-2006 articles reviewed by Whiting, et al., 2015.[2]
3. 60 PubMed or EMBASE records with "dronabinol" or "Marinol" in the title or abstract field.[3]
4. Three PubMed or EMBASE records with abstracts that refer to oral use of THC in cancer patients or HIV-infected persons.[3]

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[2] Whiting, PF, RF Wolff, S Deshpande, M Di Nisio, S Duffy, AV Hernandez, JC Keurentjes, S Lang, K Misso, S Ryder, S Schmidlkofer, M Westwood, J Kleijnen, 2015, Cannabinoids for Medical Use: A Systematic Review and Meta-analysis, JAMA, 313(24): 2456-2473. doi:10.1001/jama.2015.6358.

[3] Criterion applied to 444 primary research studies completed in human subjects.

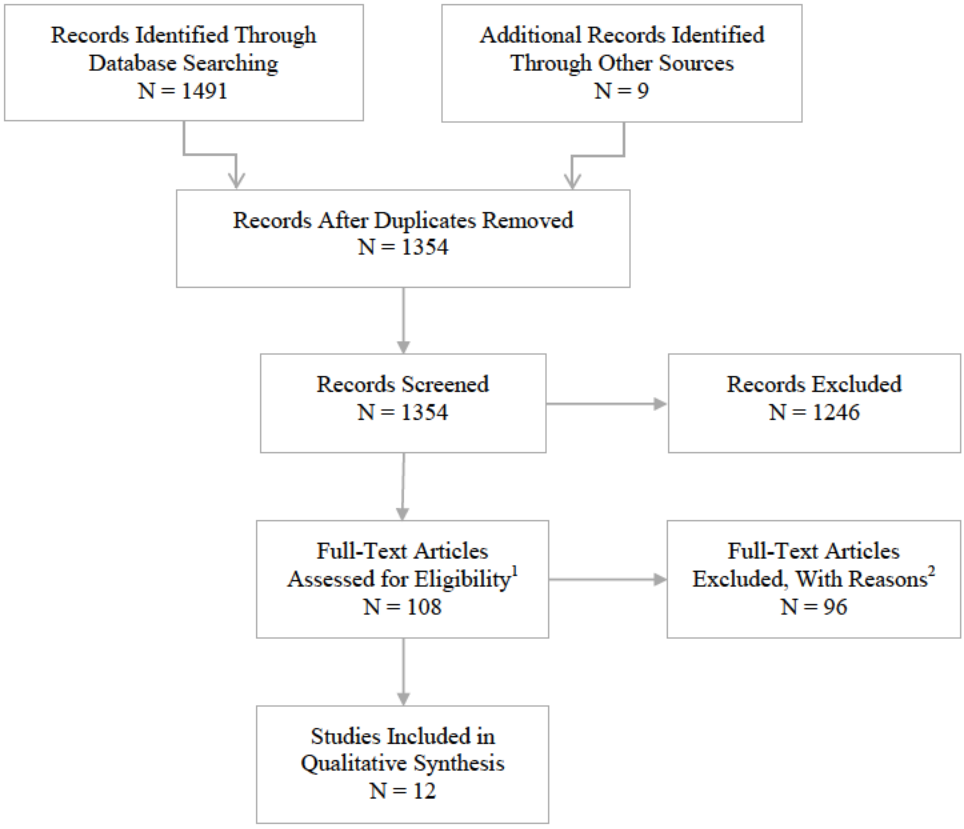
Reference ID: 3851948

After full-text review, DEPI referred five adverse event case reports to DPV and excluded 91 articles for lack of potential relevance. The criteria used to determine potential relevance required primary research results from studies of oral THC when used in cancer patients or HIV-infected persons. These inclusion criteria aimed to exclude articles exclusively about THC administered through non-oral routes and articles exclusively about THC when used for unapproved populations. These criteria help align this review with the regulatory interests of DGIEP, with one possible exception. DEPI included cancer- and HIV-related articles in qualitative synthesis, without regard to the specific clinical indications under study. Where appropriate, DEPI discusses the implications of deviations from the two approved indications, (1) anorexia and weight loss in AIDS patients and (2) nausea and vomiting from cancer chemotherapy.

See Attachment 3 for listings of the five adverse event case reports referred to DPV and the 91 articles excluded for lack of potential relevance. The latter listing includes (1) six literature reviews, (2) 27 articles about THC administered through non-oral routes, and (3) 58 articles about oral THC when used in populations not restricted to cancer or HIV-infected patients. Twelve articles, listed in Section 7 (References), remained for qualitative synthesis.

With attention to adverse events not listed under Adverse Reactions in the April 2015 draft label for dronabinol oral solution (Attachment 4), the review author (JLW) extracted general information from the 12 eligible articles to an Evidence Table (Attachment 5) and adverse event information to data tables organized according to THC exposure.

Figure 1: Systematic Review, Information Flow Diagram



1. To construct the list of 108 articles eligible for full-text review, DEPI sequentially added (1) the 21 articles cited in the Integrated Summary of Safety for NDA 205525, (2) 24 post-2006 articles reviewed by Whiting, et al., 2015,[2] (3) 60 PubMed or EMBASE records with "dronabinol" or "Marinol" in the title or abstract field, and (4) three PubMed or EMBASE records with abstracts that refer to oral use of THC in cancer patients or HIV-infected persons.
2. The 96 articles excluded for lack of potential relevance include (1) five adverse event case reports, (2) six literature reviews, (3) 27 articles about THC administered through non-oral routes, and (4) 58 articles about oral THC when used in populations not restricted to cancer or HIV-infected patients. For a complete listing, see Attachment 3: Full-text articles excluded, grouped by reason excluded. For relevance criteria, see Section 2, Review Methods and Materials.

3. REVIEW RESULTS

3.1. Controlled studies

DEPI identified six double blind placebo-controlled studies of oral THC in patients with cancer or HIV (Attachment 5, Part 1). See Section 3.3 (Adverse Events), Attachment 6 (Label Adverse Events), and Attachment 7 (Unlabeled Adverse Events) for a synopsis of the adverse events reported by these studies.

- Strasser, et al., 2006, reported adverse events experienced by adult cancer patients with weight loss. Patients received one of three treatments for six weeks, (1) dronabinol 5.0 mg/day (N=100), (2) dronabinol 5.0 mg/day and cannabidiol 2 mg/day (N=95), or (3) placebo (N=48).

- Meiri, et al., 2007, reported adverse events experienced by adult cancer patients receiving chemotherapy. Before chemotherapy, all patients received ondansetron 16 mg IV and dexamethasone 20 mg PO. Patients then received one of four treatments for five days, (1) dronabinol 5.0 mg on the first day, followed by dronabinol 10-20 mg/day (N=17), (2) dronabinol on the first day, followed by oral ondansetron 8-16 mg/day (N=16), (3) dronabinol on the first day, followed by dronabinol and ondansetron (N=17), or (4) placebo (N=13).

- Brisbois, et al., 2012, reported adverse events experienced by adult cancer patients with diminished food intake. Patients received one of two treatments for 18 days (1) dronabinol 2.5-20 mg/day (N=11) or (2) placebo (N=10).

- Reported twice in abstract form (Grunberg, et al., 2012, and Harden-Harrison, et al., 2012), one study mentioned adverse events in adult solid tumor patients on cyclophosphamide or doxorubicin chemotherapy. Before chemotherapy, all patients received palonosetron 0.25 mg and dexamethasone 10 mg. Patients then received one of two treatments for five days, (1) dronabinol 15 mg/day or (2) placebo.

- In a laboratory setting, Haney, et al., 2012, and Bedi, et al., 2010, used crossover designs to study the effects of dronabinol in 10 and 7 HIV-positive marijuana smokers, respectively. Neither study included information about adverse events.

3.2. Uncontrolled studies

DEPI identified five uncontrolled studies of oral THC in patients with cancer or HIV (Attachment 5, Part 2). Two study reports, available in abstract form only (Elder and Knoderer, 2011, and, Radiano, et al., 2011), lacked information about adverse events. A third report, published in German with English abstract, contained information about seven dronabinol-treated patients. The final two studies described adverse events experienced by dronabinol-treated patients. Specifically,

- Reporting in abstract form, Allen, et al., 2009, studied 31 adults with primary glioma treated with dronabinol 10 mg/day for the three days during chemotherapy and 2.5 mg/day between chemotherapy treatments.

- Dejesus, et al., 2007, reviewed the medical records of 155 HIV/AIDS patients, with anorexia and weight loss, treated with dronabinol, mean daily dose 9.6-12.1 mg, for at least three months.

For a synopsis of the adverse events reported by these two studies, see Attachment 6 (Label Adverse Events) and Attachment 7 (Unlabeled Adverse Events).

3.3. Adverse Events

Four controlled studies and three uncontrolled studies, reporting on 176 and 134 THC-exposed patients, respectively, mentioned at least one adverse event also appearing under Precautions or Adverse Reactions on the current Marinol label[4] (Attachment 6). Frequent events included diarrhea, nausea, vomiting, dizziness, and headache. Some adverse events were more frequent in THC-exposed than control, for example, vomiting as a serious adverse event, eight (8%) of 100 exposed vs. one (2%) of 48 control patients (Strasser, et al., 2006).

Attachment 7 lists the unlabeled adverse events discovered by DEPI in post-2006 medical literature. Table 1 restricts this list to controlled studies and adverse events reported in more than one THC-exposed patient. The adverse events reported only once include (1) chest pain, (2) gait disturbance, (3) edema, (4) pneumonia, (5) Candida infection, (6) low blood count, (7) insomnia, and (8) vaginal discharge. Adverse events that occurred more frequently in exposed than control patients included quality of life decreased (reported as a serious worsening of general well-being), death, dyspnea, neoplasm progression, pain, and fatigue.

Strasser, et al., 2006, provided 100 (57%) of the 176 exposed patients shown in Table 1. In Strasser, et al., 2006, THC vs. placebo differences were not statistically significant, for example, p-values (Fisher's Exact Test, two-sided), 0.17, 0.72, 0.50, 0.33, and 0.43 for quality of life decreased, dyspnea, neoplasm progression, pain, and fatigue, respectively.

Strasser, et al., 2006, contained inconsistent information about death. A paragraph listing serious adverse events reported death in six of 100 THC vs. one of 48 control patients (Table 1; exact p-

[4] MARINOL® (dronabinol) Capsules, June 21, 2006, Drugs@FDA, Retrieved from http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm on October 15, 2015.

value, 0.43), whereas the study flow diagram showed eight and one deaths (exact p-value, 0.27).

Table 1: Unlabeled adverse event occurrences in placebo-controlled studies, by exposure group, oral Δ^9-tetrahydrocannabinol (THC) vs. placebo (PLO).

	Strasser, 2006		Meiri, 2007		Brisbois, 2011		Grunberg, 2012	
	THC	PLO	THC	PLO	THC	PLO	THC	PLO
Number exposed	100	48	34	13	11	10	31	31
Adverse Events, N [1]								
quality of life decreased [2]	9	1						
Death	6	1						
Dyspnea	7	2			3	1		
neoplasm progression	8	2						
Pain	17	5			2	1		
Fatigue	14	4	2	1	1	2	17	11
Dehydration	3	1	0	0	1	1		
Constipation	7	2	1	0	0	3	14	11
Anemia	14	6						
Urticarial					3	3		
Fever	2	2			0	1		

1. MedDRA preferred terms, sorted from high to low values for the common relative risk, THC vs. PLO.
2. Reported as a serious worsening of general well-being.

4. DISCUSSION

The post-2006 medical literature contained scant information about the safety of dronabinol in cancer or HIV-infected patients. A DEPI search identified 12 publications, six available only as abstracts. DEPI tabulated the adverse events reported for 176 and 134 patients exposed to THC in four controlled and three uncontrolled studies, respectively. Except as noted below, the adverse event experiences of these patients matched the labelled safety profile for dronabinol.

One randomized, double blind, placebo-controlled clinical study (Strasser, et al., 2006) used oral THC (2.5 mg twice daily for six weeks) to treat cancer-related anorexia-cachexia syndrome. A data safety monitoring board closed this study because of "insufficient differences in the primary end point" (change in appetite). Important unlabeled adverse events were more frequent in THC-treated patients (Table 1). The study authors correctly reported that these treatment-related differences in toxicity were not statistically significant. This study did not restrict patients to the approved dronabinol indication, nausea and vomiting from chemotherapy. One-half of patients had not received chemotherapy during the four weeks before study entry. This novel cancer indication, poor appetite, limits the relevance of this study for regulatory purposes.

The four controlled and three uncontrolled studies with information about adverse events varied in quality. Each of the four controlled studies that reported adverse events used randomization and double blind placebo control (Strasser, et al., 2006; Meiri, et al., 2007; Brisbois, et al., 2011; Grunberg, et al., 2012). Therefore, these studies used research methods designed to provide valid safety information. However, one of the four controlled studies (Grunberg, et al., 2012) reported results in abstract form only. A second study (Brisbois, et al., 2011) was not specifically designed to test the efficacy and safety of dronabinol treatment for a medical problem. Authors generally restricted reporting to frequent adverse events. For example,

Reference ID: 3851948

Strasser, et al., 2006, reported only adverse events occurring in more than ten patients and serious adverse events occurring in at least five patients. These adverse events included statistically non-significant imbalances in death, dyspnea, and neoplasm progression. However, these findings are inconsistent with the greater body of evidence. FDA's 2006 postmarket safety review lacked mention of these events. The meta-analysis, by Whiting, et al., 2015, failed to find imbalances in these adverse events. Meiri, et al., 2007, reported adverse events occurring in two or more patients. Finally, the studies covered by this review contained too few patients for confident detection of rare adverse events.

The three uncontrolled studies lacked quality as well. Results from two studies were available in abstract form only (Zutt, et al., 2006; Allen, et al., 2009). The third study (DeJesus, et al., 2007) obtained adverse event information by means of retrospective chart review.

Because of the availability of safer and more effective treatments, the National Comprehensive Cancer Network NCCN clinical practice guideline for antiemesis does not recommend dronabinol for preventing CINV.[5] Rather, the NCCN accepts dronabinol 5-10 mg every 3 or 6 hours for breakthrough nausea and vomiting only. Likewise, the Marinol label approves dronabinol for nausea and vomiting from cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Therefore, FDA and NCCN agree on a secondary role for dronabinol in CINV.

Most studies covered by this review used conventional dronabinol dosing, 5-20 mg/day. Two studies in marijuana-experienced HIV-infected patients used dronabinol at higher daily doses, 40 mg/day as 10 mg four times daily (Haney, et al., 2007; Bedi, et al., 2010). No study used dronabinol at the highest single dose (15 mg/m^2) currently approved for chemotherapy-induced nausea and vomiting. The maximum single dose of 15 mg/m^2 corresponds to 25-30 mg in average-sized adults.

FDA and NCCN dosing guidelines differ only in detail. As noted above, NCCN advises simply 5-10 mg every 3 or 6 hours. The Marinol label advises 5 mg/m^2 initially, four to six times daily, and, if ineffective and tolerated, carefully titrated in 2.5 mg/m^2 increments to the maximum 15 mg/m^2 dose. These minor differences between the Marinol label and NCCN guideline possess little clinical relevance.

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

5. CONCLUSION

The scant information in medical literature published in 2006 or later about dronabinol, when used in cancer or HIV-infected patients, describes a safety profile consistent with the Prescribing Information proposed for dronabinol oral solution. Results from a study published in 2006

[5] Todaro, B, 2012, Cannabinoids in the Treatment of Chemotherapy-Induced Nausea and Vomiting, J Natl Compr Canc Netw, 10:487-492.

Ettinger, DS, MJ Berger, J Aston, et al. NCCN Clinical Practice Guidelines in Oncology for Antiemesis. Version 2, 2015. Retrieved from www.nccn.org on October 19, 2015.

cautions against the use of dronabinol for cancer-related anorexia-cachexia syndrome. However, the results from this study do not constitute a new safety signal in regards to approved dronabinol indications.

6. RECOMMENDATION

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

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E Wu / N Miles / R Levin (DPV)

Attachment 1: DGIEP consult request to OSE

1. Please review the postmarketing FAERS reports and the literature 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.

2. Marinol is approved in doses up to 15 mg/m^2 for the prevention of nausea and vomiting associated with cancer chemotherapy and adverse events are dose related, especially above 7 mg/m^2. During the pre-NDA meeting the sponsor noted that doses of 7 mg/m^2 and above are not consistent with current clinical use. In your evaluation of the postmarketing FAERS data and literature, please include an assessment of whether doses above 7 mg/m^2 are associated with excess risk.

3. The Contraindications section of the sponsor's proposed PI for dronabinol oral solution states: [redacted (b) (4)] However, it is not clear from the description of adverse reactions, whether hypersensitivity to dronabinol [redacted (b) (4)] has occurred or is a theoretical risk. Please provide information on risk of systemic hypersensitivity reactions (e.g., anaphylaxis) to the product.

Attachment 2: Literature search strategies

A PubMed search, completed on September 22, 2015, using the search strategy shown below, identified 422 articles.

> (((((((((Cesamet) OR nabilone) OR marinol) OR dronabinol)) OR "cannabinoids"[MeSH Major Topic]) AND ((Case Reports[ptyp] OR Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Meta-Analysis[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Controlled Clinical Trial[ptyp]) AND ("2006/01/01"[PDat] : "2015/12/31"[PDat]) AND Humans[Mesh]))) AND ((adverse effects[MeSH Subheading] OR complications[MeSH Subheading] OR drug effects[MeSH Subheading] OR "adverse effect" OR "adverse effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse outcome" OR "adverse outcomes" OR safe OR safety OR side effect* OR undesirable effect* OR treatment emergency OR tolerability OR toxicity OR ADRS)))

An EMBASE search, completed on September 22, 2015, using the search strategy shown below, identified 2123 articles.

> 'dronabinol'/exp OR 'dronabinol' AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR (safe OR safety OR 'side effect$' OR undesirable AND effects$) OR 'treatment emergency' OR tolerability OR toxicity OR adrs OR adverse NEXT/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes) OR 'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'side effect'/exp OR 'side effect')

Attachment 3: Full-text articles excluded, grouped by reason excluded

Part 1: Adverse event case reports referred to the OSE Division of Pharmacovigilance

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Attachment 4: Adverse Reactions in April 2015 draft label for dronabinol oral solution.

		MedDRA Coding		
Adverse Reaction	Freq	PT	SOC	SOC Name
abdominal pain	≥1%	10000081	10017947	Gastrointestinal disorders
amnesia	≥1%	10001949	10029205	Nervous system disorders
anorexia	<1%	10061428	10018065	General disorders and administration site conditions
anxiety/nervousness	≥1%	10002855	10037175	Psychiatric disorders
asthenia	≥1%	10003549	10018065	General disorders and administration site conditions
ataxia	≥1%	10003591	10029205	Nervous system disorders
chills	<1%	10008531	10018065	General disorders and administration site conditions
confusion	>1%	10010305	10029205	Nervous system disorders
				(b) (4)
cough	<1%	10011224	10038738	Respiratory, thoracic and mediastinal disorders
depersonalization	≥1%	10012357	10037175	Psychiatric disorders
depression	<1%	10012378	10037175	Psychiatric disorders
diarrhea	<1%	10012735	10017947	Gastrointestinal disorders
dizziness	≥1%	10013573	10029205	Nervous system disorders
euphoria	≥1%	10015535	10037175	Psychiatric disorders
fecal incontinence	<1%	10016092	10017947	Gastrointestinal disorders
flushing	<1%	10016825	10040785	Skin and subcutaneous tissue disorders
				(b) (4)
headache	<1%	10019211	10029205	Nervous system disorders
hepatic enzyme elevation	<1%	10062685	10022891	Investigations
hypotension	<1%	10021097	10047065	Vascular disorders
malaise	<1%	10025482	10018065	General disorders and administration site conditions
myalgias	<1%	10028411	10028395	Musculoskeletal and connective tissue disorders
nausea	≥1%	10028813	10017947	Gastrointestinal disorders
nightmares	<1%	10029412	10037175	Psychiatric disorders
palpitations	≥1%	10033557	10007541	Cardiac disorders
paranoid reaction	≥1%	10033864	10037175	Psychiatric disorders
rhinitis	<1%	10039083	10038738	Respiratory, thoracic and mediastinal disorders
sinusitis	<1%	10040753	10038738	Respiratory, thoracic and mediastinal disorders
somnolence	≥1%	10041349	10029205	Nervous system disorders
speech difficulties	<1%	10041466	10029205	Nervous system disorders
sweating	<1%	10020642	10040785	Skin and subcutaneous tissue disorders
tachycardia	≥1%	10043071	10007541	Cardiac disorders
thinking abnormal	≥1%	10043431	10029205	Nervous system disorders
tinnitus	<1%	10043882	10029205	Nervous system disorders
vasodilation/facial flush	≥1%	10016825	10047065	Vascular disorders
vision difficulties	<1%	10047571	10015919	Eye disorders
vomiting	≥1%	10047700	10017947	Gastrointestinal disorders

Attachment 5: Evidence tables. See Attachments 6 and 7 for adverse event evidence.

Study Design: Randomized, placebo-controlled studies of oral THC

Reference	ISS [1]	Source [2]	Population	Objective of Study	AEs [3]	N [4]	Oral THC Dosing
Strasser 2006 [5]	N	PubMed	adult cancer patients losing weight	comparative efficacy and safety of THC and THC plus cannabidiol for treatment of cancer-related anorexia and cachexia	Y	100	THC 2.5 mg BID for 6 weeks
Meiri 2007 [6]	Y	PubMed	adult cancer patients receiving emetogenic chemotherapy	comparative efficacy and safety of extended dronabinol treatment for prevention of nausea and vomiting delayed 2-5 days after chemotherapy	Y	34	dronabinol (Marinol) 2.5 mg BID on day of chemotherapy, with or without dronabinol 2.5-5.0 mg QID for the 4 days after chemotherapy
Brisbois 2011	N	PubMed	adult cancer patients with diminished food intake	effects of dronabinol on taste and smell	Y	11	dronabinol (Marinol) 2.5 mg BID, increased to maximum of 20 mg per day, for 18 days
Grunberg 2012; Harden-Harrison 2012 (ABSTRACT)	N	EMBASE	adult solid tumor patients receiving cyclophosphamide or doxorubicin	comparative efficacy and safety of oral dronabinol for prevention of chemotherapy-induced nausea and vomiting	Y	31	dronabinol 5 mg TID for 5 days
Haney 2007 [7]	Y	PubMed	HIV-positive marijuana smokers	effects of dronabinol on caloric intake and body weight	N	10	dronabinol (Unimed Pharmaceuti-cals) 5 or 10 mg QID for 4 days
Bedi 2010 [7]	Y	PubMed	HIV-positive marijuana smokers	effects of dronabinol on caloric intake and body weight	N	7	dronabinol (Unimed Pharmaceuti-cals) 5 mg QID for 2 days, increased to 10 mg QID for 14 days

Study Design: Uncontrolled case series of patients treated with oral THC

Reference	ISS [1]	Source [2]	Population	Objective of Study	AEs [3]	N [4]	Oral THC Dosing
Zutt 2006 (GERMAN with English Abstract)	N	PubMed	patients with malignant melanoma and liver metastases	efficacy and safety of dronabinol for treatment of poor appetite and nausea	Y	7	dronabinol (Marinol)
Allen 2009 (ABSTRACT)	N	EMBASE	adults with primary glioma treated with adjuvant chemotherapy	efficacy and safety of dronabinol for treatment of chemotherapy-induced nausea and vomiting	Y	31	dronabinol 5 mg BID from 24 hours before to 48 hours after chemotherapy administration, reduced to 2.5 mg daily between chemotherapy administrations
Elder 2011 (ABSTRACT)	N	EMBASE	≤18 year-old cancer patients who received ≥1 dronabinol dose	pediatric efficacy and safety of dronabinol for treatment of chemotherapy-induced nausea and vomiting	N	UNK	dronabinol
Radiano 2011 (ABSTRACT)	N	EMBASE	>3 year-old stem-cell-transplant patients	characteristics of patients treated with oral THC for chemotherapy-induced nausea and vomiting	N	UNK	THC 5 mg in olive oil under tongue BID
Dejesus 2007	Y	ISS	dronabinol-treated HIV/AIDS patients with anorexia and weight loss	efficacy and safety of dronabinol for treatment of poor appetite and weight loss	Y	155 96 [8]	dronabinol (Marinol), mean daily dose, 9.6-12.1, depending on follow-up time, for 3-12 months

ABBREVIATIONS: AEs, Adverse Events; BID, twice daily; ISS, Integrated Summary of Safety; QID, four times daily; THC, Δ^9-tetrahydrocannabinol; TID, three times daily; UNK, unknown (not reported)

1. Source cited in the Integrated Summary of Safety (ISS) for NDA 205525, Y=Yes, N=No.
2. Method used to find source.
3. Adverse Events (AEs) reported, Y=Yes, N=No.
4. Number of patients who received oral THC.
5. Oral THC plus cannabidiol comparator studied, in addition to placebo.
6. Ondansetron compartor studied, in addition to placebo.
7. Crossover design.
8. 155 patients evaluated at different time points 3-12 months after first dronabinol use recorded after January 11, 1993; 96 patients evaluated at three months.

Reference ID: 3851948

Attachment 6: Labeled adverse events reported, by study group

	Study-specific Exposure Categories [2]												
Adverse Event (MedDRA System Organ Class and Preferred Term) [1]	Strasser 2006			Meiri 2007			Brisbois 2011		Grunberg 2012		Zutt 2006	Allen 2009	Dejesus 2007
	THC	ACT	PLO	THC	ACT	PLO	THC	PLO	THC	PLO	THC	THC	THC
N	100	95	48	34	16	13	11	10	31	31	7	31	96 [3]
Gastrointestinal													
(b) (4) abdominal pain							1	2					
diarrhea	7	6	2	4	1	1	2	0	13	6			
diarrhea SAE [4]	2	3	0										
nausea or vomiting	21	23	11				5	2					
vomiting SAE [4]	8	8	1										
General													
asthenia				2	1	1							
Cardiovascular													
palpitations							1	0					
Nervous System													
confusional state							0	1					1
thinking abnormal													1
dizziness	11	9	7	1	1	0			14	7	7		
headache				0	3	0	2	0	16	16			
seizure							1	0					
somnolence												UNK	1
Psychiatric													
anxiety													
depersonalization													1
euphoric mood													1
paranoia													1

1. Events appearing under the Precautions or Adverse Reactions on the current Marinol label, MARINOL® (dronabinol) Capsules, June 21, 2006, Drugs@FDA, Retrieved from http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm on October 15, 2015.
2. THC – oral Δ^9-tetrahydrocannabinol; ACT – active comparator (oral THC plus cannabidiol for Strasser 2006; ondansetron for Meiri 2007); PLO – placebo.
3. Results at three months.
4. Serious adverse event.

Reference ID: 3851948

Attachment 7: Unlabeled adverse events reported, by study exposure

	Study-specific Exposure Categories [2]										
Adverse Event (MedDRA System Organ Class and Preferred Term) [1]	Strasser 2006			Meiri 2007			Brisbois 2011		Grunberg 2012		Allen 2009
	THC	ACT	PLO	THC	ACT	PLO	THC	PLO	THC	PLO	THC
N	100	95	48	34	16	13	11	10	31	31	31
Blood											
anemia	14	9	6								
Gastrointestinal											
constipation	7	6	2	1	2	0	0	3	14	11	
General											
chest pain				1	2	0					
death	6	4	1								
fatigue	14	16	4	2	1	1	1	2	17	11	4
gait disturbance							1	0			
edema							1	0			
pain	17	11	5				2	1			
fever	2	3	2				0	1			
Infection											
pneumonia							1	1			
Candida infection							1	0			
Investigation											
blood count							1	0			
quality of life decreased	9	2	1								
Metabolism											
dehydration	3	1	1				1	1			
hyperglycemia				0	2	0					
Neoplasm											
neoplasm progression	8	5	2								
Psychiatric											
Insomnia				0	2	0	1	0			
Reproductive System											
vaginal discharge							1	0			
Respiratory											
dyspnea	7	9	2				3	1			
Skin											
urticaria							3	3			
Procedure											
therapy cessation											11

1. Events not appearing under the Precautions or Adverse Reactions on the current Marinol label, MARINOL® (dronabinol) Capsules, June 21, 2006, Drugs@FDA, Retrieved from http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm on October 15, 2015..
2. THC – oral Δ^9-tetrahydrocannabinol; ACT – active comparator (oral THC plus cannabidiol for Strasser 2006; ondansetron for Meiri 2007); PLO – placebo.

Reference ID: 3851948

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/s/

JOEL L WEISSFELD
11/24/2015

SUKHMINDER K SANDHU
11/24/2015

DAVID C SHIH
11/25/2015

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 27, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Maureen Dewey, RPM
DGIEP

Subject: QT-IRT Consult to NDA 205525

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 7/15/2015 regarding your questions of the QT effect assessment of dronabinol. The QT-IRT received and reviewed the following materials:

- Your consult
- Highlight of clinical pharmacology and cardiac safety
- Proposed label

QT-IRT Comments for DGIEP

Specific questions for QT-IRT:

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 the ΔΔQTc-timecourse for the moxifloxacin was not demonstrated;
3. Inconsistent results were presented in the paper: there are several upper bounds of the 90% CIs of ΔΔQTcI 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.

2. 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).

3. 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.

BACKGROUND

NDA 205525 is a 505(b)(2) application for dronabinol oral solution (4.25 mg/0.85 ml) copackaged with a dosing syringe for the a) treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and b) anorexia associated with weight loss in patients with AIDS.

Dronabinol oral solution is a new formulation of dronabinol, and contains synthetic delta-9-tetrahydrocannabinol (delta-9-THC). The applicant is relying for safety and efficacy on Marinol (dronabinol capsules) approved on May 31, 1985 as the reference listed drug.

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 discuss the QT prolonging potential of dronabinol.

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

It appears that Sellers' paper followed the sativex TQT protocol. Although the authors claimed that "*For THC/CBD spray, most placebo-corrected changes from baseline values were less than 5 ms, ranging from 4.1 to 5.2ms for THC/CBD spray 8 sprays and from 5.5 to 6.2 ms for THC/CBD spray 24/36 sprays. The upper bounds of the 90% CIs for both THC/CBD spray treatment groups were below the 10ms thresholds at all time-points, indicating no effect on cardiac repolarization*", the results from their figure showed there are multiple upper bounds of the 90% CIs for THC/CBD 8-spray treatment group that were above 10 ms (see the following figure). The rising phase of the ΔΔQTc-timecourse for the moxifloxacin treatment group is also missing, making the ECG assay sensitivity in this study questionable. Although the authors claimed "*The slopes for placebo-corrected change in QTcI from baseline versus THC, 11–OH–THC, and CBD plasma concentrations were flat to negative. The upper bounds of the 95% CIs for predicted change in QTcI at average THC, 11–OH–THC, and CBD Cmax (at all THC/CBD spray doses) were less than 10 ms (≤5.821 ms)*", no detailed information was provided in the paper.

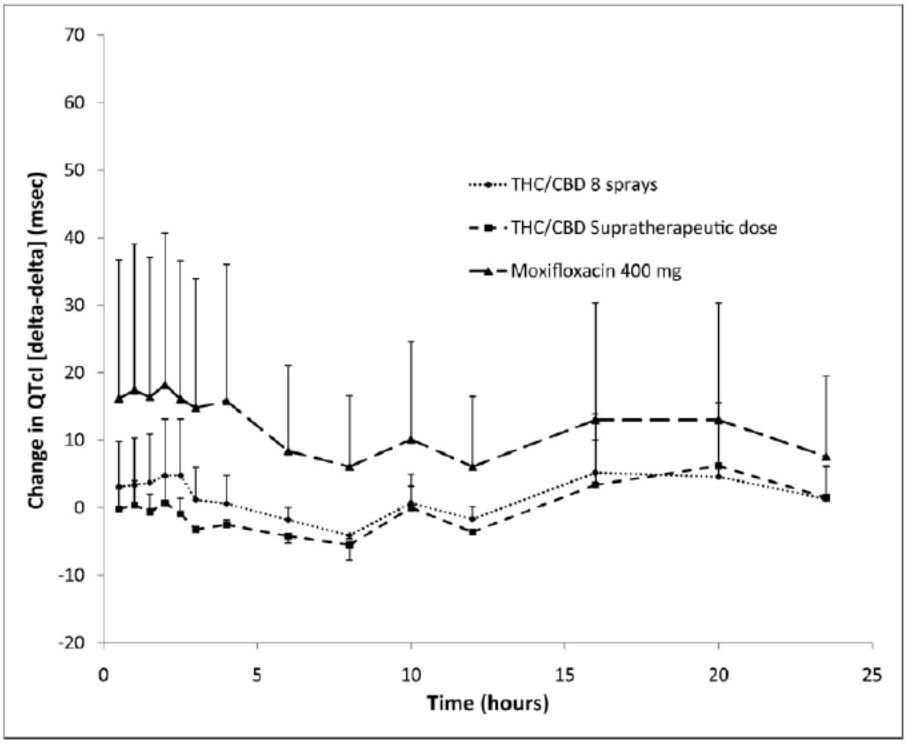


Figure 1. Placebo-corrected, change from baseline in QTcI (ms)—Estimated from mixedmodel analysis of variance (90% CI).

It appears that the THC exposures in the TQT study (with mean Cmax of 3.1 and 9.2 ng/mL for the 8-spray and 24/36-spray treatment) cover the range of exposure expected for the dronabinol appetite stimulation indication [i.e., with mean Cmax of 1.32 to 7.88 ng/mL for 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/m^2 given four to six times per day, which is equivalent to dronabinol oral

solution 4.25 to 12.75 mg/m^2 four to six times per day] and the exposures in this TQT study is expected to be inadequate to cover the therapeutic exposure for the antiemetic indication.

Reviewer's comments: It is unclear whether there is a significant slope for the concentration-QTc relationship.

Thank you for requesting our input into the development of this product under NDA 205525. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
10/27/2015

NORMAN L STOCKBRIDGE
10/27/2015

M E M O R A N D U M

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

DATE: 8/4/2015

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: NDA 205525

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Worldwide Clinical Trials Drug Development Solutions, Clinical Research Services	2455 N.E. Loop 410, Suite 150, San Antonio, TX 78217

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/s/

SHILA S NKAH
08/04/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application:	205525
Application Type:	NDA
Name of Drug/Dosage Form:	dronabinol oral solution
Applicant:	Insys Therapeutics
Receipt Date:	06/01/2015
Goal Date:	04/01/2015

1. Regulatory History and Applicant's Main Proposals

NDA 205525 is a 505(b)(2) application for dronabinol oral solution (4.25 mg/0.85 ml). The product is copackaged with a dosing syringe and the applicant proposes the following indications:

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.

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

The applicant is relying for safety and efficacy on Marinol (dronabinol capsules) approved on May 31, 1985 as the reference listed drug. The Marinol label is not currently in PLR format.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. **Format the Table of Contents as described in the SRPI.**
2. **The established pharmacologic class (EPC) does not need to be included in the Indications and Usage statement in the FPI, only in Highlights.**
3. **Please correct the use of cross-referencing throughout.**

Reference ID: 3802636

a. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. See comment regarding Section 2.3 cross-reference to (8.5)

b. When a section contains subsections, the cross-reference to that section should cross-reference to the specific subsection containing the additional information (e.g., 12.x). For example, see comment in section 5.2 Cardiac Disorders.

4. Insert required statement in Section 6.1:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

5. You have omitted a Clinical Studies section. However, the Marinol PI contains efficacy information from the clinical trials conducted with that product in a subsection titled "Clinical Trials" in the CLINICAL PHARMACOLOGY section.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by ***September 1, 2015.*** The resubmitted PI will be used for further labeling review.

Reference ID: 3802636

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

Currently, there is no white space before each major heading, please correct.

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

Reference ID: 3802636

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

NO 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Reference ID: 3802636

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

Reference ID: 3802636

For example in Section 2.3: the correct cross-reference should be [see SPECIFIC POPULATIONS (8.5) instead of "Geriatric Use".

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

    Comment:

NO 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

    Comment:

Reference ID: 3802636

Appendix A: Format of the Highlights and Table of Contents

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 [text]
  2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 [text]
  5.2 [text]
6 ADVERSE REACTIONS
  6.1 [text]
  6.2 [text]
7 DRUG INTERACTIONS
  7.1 [text]
  7.2 [text]
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Labor and Delivery
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
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  12.3 Pharmacokinetics
  12.4 Microbiology
  12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
  14.1 [text]
  14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3802636

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/s/

MAUREEN D DEWEY
08/06/2015

KEVIN B BUGIN
08/06/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 205525 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Syndros (proposed) Established/Proper Name: dronabinol Dosage Form: oral solution Strengths: 4.25 mg/0.85 mL		
Applicant: Insys Therapeutics Attn: Stephen Sherman, Vice President Regulatory Affairs 1333 South Spectrum Blvd, Suite 100 Chandler, AZ 85286 Agent for Applicant (if applicable):		
Date of Application:06/01/2015 Date of Receipt: 06/01/2015 Date clock started after UN:		
PDUFA Goal Date: April 1, 2015	Action Goal Date (if different):	
Filing Date: 07/31/2015	Date of Filing Meeting: 07/16/2015	

Chemical Classification (original NDAs only) :

☐ Type 1- New Molecular Entity (NME); NME and New Combination

☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination

☒ Type 3- New Dosage Form; New Dosage Form and New Combination

☐ Type 4- New Combination

☐ Type 5- New Formulation or New Manufacturer

☐ Type 7- Drug Already Marketed without Approved NDA

☐ Type 8- Partial Rx to OTC Switch

Proposed indications/Proposed change(s):

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

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Type of Original NDA: AND (if applicable)	☐ 505(b)(1) ☒ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)

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Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☒
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☒ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number: IND075228	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		

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Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	Type 3: New Dosage Form and New Combination RS POST RTF
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes

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	☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☒	☐		**Marinol designated 1/15/1991 approved orphan indication for "treatment of anorexia associated with weight loss in patients with AIDS"**

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				Exclusivity expired on 12/22/1999
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	Exclusivity expired
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: **3 years** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the	

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application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	Paragraph II Certification submitted
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21***	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	FC certification included.
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: **6/17/2015**	☒	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**

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PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? Pediatric Studies were not required to be submitted. Indication of Anorexia Associated Weight Loss in pts with AIDS PARTIAL WAIVER: 0 – 14 years PARTIAL DEFERAL: 15-17 years Indication of CINV FULL DEFERRAL: all ages ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	7/17/2015
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/***	☐	☒	☐	

2 http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

3 http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

OSI/DSC/PMSB via the CDER OSI RMP mailbox				
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consults and dates sent:*** ***DPMH (6/4/2015)*** ***CSS (6/19/2015)*** ***QT-IRT (7/21/2015)*** ***CDRH (6/8/2015)*** ***Micro (6/17/2015)*** ***DMEPA (6/9/2015)***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date:** ***September 20, 2010*** ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): ***PreNDA: April 17, 2012*** ***Prelim Comments March 7, 2013*** ***WRO December 15, 2013*** ***General Advice Letter December 10, 2014*** ***Agreements made for NDA*** ***If yes, distribute minutes before filing meeting***	☒	☐		

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Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

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ATTACHMENT

MEMO OF FILING MEETING

DATE: 07/16/2015

BACKGROUND: NDA 205525

PROPRIETARY NAME: Syndros (proposed 7/17/2015)

ESTABLISHED/PROPER NAME: dronabinol

DOSAGE FORM/STRENGTH: oral solution 4.25 mg/0.85 ml

APPLICANT: Insys Therapeutics, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

i) Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments, and

ii.) anorexia associated with weight loss in patients with AIDS.

BACKGROUND:

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

(1) Nausea and vomiting associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetics
(2) Anorexia associated with weight loss in patients with AIDS

On August 12, 2014, Insys Therapeutics submitted NDA 205525 dronabinol oral solution (referenced IND 075228) pursuant to the 505(b)(2) regulatory pathway, proposing NDA 018651 Marinol (dronabinol capsules) as the reference listed drug. The reference listed product Marinol® 5 mg capsules has been approved since 1985 for the same indications.

The applicant submitted three comparative bioavailability and bioequivalence studies (INS-08-008, INS-10-012, and the pivotal study INS-12-015), a required abuse liability study in support of the NDA. A label comprehension study was also submitted. The requirement to submit an ISE was waived in the pre-NDA meeting due to the presence of only one pivotal BE study. The sponsor did submit an ISS. A food effect study was requested by not required (EOP2 meeting).

On October 10, 2014, a Refuse to File correspondence was issued because the application failed to address the requirements under the Pediatric Research Equity Act (PREA), for the application provided an incomplete or inadequate pediatric study plan.

A resubmission after RTF was received on June 1, 2015.

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REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dewey	YES
	CPMS/TL:	Kevin Bugin (Acting)	YES
Cross-Discipline Team Leader (CDTL)	Joette Meyer		YES
Division Director/Deputy	Donna Griebel Andrew Mulberg Joyce Korvick Dragos Roman		YES YES YES YES
Office Director/Deputy	Julie Beitz		N
Clinical	Reviewer:	Wen-Yi Gao	YES
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	YES
	TL:	Sue Chih Lee	YES
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Yeh-Fong Chen	YES
	TL:		

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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fang Cai	YES
	TL:	David Joseph	YES
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Danuta Gromek-Woods	YES
	RBPM:	Heather Strandberg	NO
• Drug Substance	Reviewer:	Jefferey Medwid	NO
• Drug Product	Reviewer:	Hitesh Shroff	NO
• Process	Reviewer:	Kelly Forney-Stevens	NO
• Microbiology	Reviewer:	Johnathan Swoboda	YES
• Facility	Reviewer:	Vipyl Dholakia	NO
• Biopharmaceutics	Reviewer:	Vincent Duan	YES
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	NO
	TL:	Marcia Britt Williams	NO
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Matthew Barlow	NO
	TL:	Kendra Wilkinson	NO
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Matthew Barlos	YES
	TL:	Kendra Wilkinson	YES
OSE/DRISK	Reviewer:	DPV: Eileen Wu RX Use: Mohamed Mohamoud DEPI: Sukh Sandhu DRISK: Jamie Wilkins Parker	NO
	TL:	Nicolas Miles Patty Green Joel Weissfeld Robert Pratt	NO
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Martin Rusinowitz	YES
	TL:	Michael Klein	NO
Other reviewers/disciplines			
DPMH	Reviewer:	Erica Wynn/Carol Kasten	YES
	TL:	Alyson Karesh/ Tamara Johnson	YES
Other attendees	Denise Pica-Branco, DMPH Brian Strong, CPMS Alex Winiarski		YES

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies): 505(b)(2) application relying on Agency's finding of safety and efficacy of Marinol. The NDA contains the following comparative BA studies: **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 ***Pivotal** **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	
• Per reviewers, are all parts in English or English	☒ YES

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translation? **If no**, explain:	☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

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CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Reference ID: 3802631

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

Reference ID: 3802631

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: tbd **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): November 4, 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

Reference ID: 3802631

Milestone Meetings per Standard Review:

Meeting	DRG	Date
Filing Meeting	By Day 45	July 16, 2015
Planning Meeting		N/A
Filing Day 60		July 31, 2015
74 Day Letter		August 14, 2015
120 Day Safety Update		September 29, 2015
Mid Cycle Meeting	Month 5	November 4, 2015
Labeling Planning Meeting	1-2 weeks after Midcycle	November 17, 2015
505(b)2 Committee	60 Days Prior to Action	February 1, 2016
Wrap Up Meeting	7 weeks prior to Action	February 12, 2016
Send labeling and PMR	By month 9	March 1, 2016
PeRC	6 weeks prior to Action	February 19, 2016
Primary Reviews due	Month 8.75	February 22, 2016
Secondary Reviews due	Month 9	March 1, 2016
OC clearance of confirmatory TB-EER	30 Days prior to AP	March 2, 2016
CDTL Review due	3 weeks prior to PDUFA	March 11, 2016
DD Review due/Issue Action Letter	Month 10	April 1, 2016

Reference ID: 3802631

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/s/

MAUREEN D DEWEY
08/06/2015

KEVIN B BUGIN
08/06/2015

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 16, 2012

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Sponsor questions regarding abuse studies
Dronabinol oral solution (4.25 mg/dose, 5 mg/ml solution)
IND 75, 228
Indication: Treatment of nausea/vomiting associated with cancer chemotherapy in patients who (b) (4) to conventional anti-emetic treatments
Sponsor: Insys Therapeutics

Materials reviewed: Sponsor submission: "In vitro abuse potential evaluation plan for oral dronabinol solution" (10/2/12)

Background:

This memorandum responds to a consult request by the Division of Gastroenterology and Inborn Errors Products to respond to several questions posed by Insys Therapeutics regarding their plan for evaluating the abuse potential of their Dronabinol Oral Solution drug product. Dronabinol is delta-9-tetrahydrocannabinoid, a cannabinoid agonist at CB1 and CB2 receptors.

The Dronabinol Oral Solution product is proposed for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments. The proposed dose is 4.25 mg/dose, utilizing a 5 mg/ml solution (which contains 50% w/w dehydrated ethanol). This formulation is different from that of the currently marketed oral drug products containing dronabinol (Marinol and its generic products) since they do not contain ethanol and are instead formulated with sesame oil ((b) (4)).

CSS previously attended the EOP2 meeting on June 16, 2009, and the pre-NDA meeting on March 19, 2012. At these meetings, CSS provided feedback regarding the assessment of the abuse potential of the dronabinol oral solution.

CSS Responses to Sponsor Questions:

Question #1

Does the Agency agree no in vitro experimental work is required to evaluate the abuse potential for the oral delivery route?

CSS Response:

Yes. It is not necessary to conduct *in vitro* studies to evaluate the abuse potential of the Dronabinol Oral Solution by oral route.

Question #2

Does the Agency agree with the proposed in vitro experimental work to compare the abuse potential for the Dronabinol Oral Solution and Marinol products?

CSS Response:

Yes, we agree with the proposed *in vitro* studies as summarized in Table 2.

Question #3

Will data from the in vitro testing battery (i.e., injectability, syringibility, and dried residue), and a comprehensive literature review be sufficient to adequately address the likelihood of abuse?

CSS Response:

No. Although the *in vitro* studies will provide necessary information regarding the feasibility of preparing a sample for injection and a sample suitable for smoking, they will not be sufficient to assess the likelihood of abuse relative to Marinol. As noted below in Question #4, a human abuse potential study will be required.

Question #4

Does the Agency agree that no clinical abuse liability studies need to be performed?

Reference ID: 3217957

CSS Response:

No. A human abuse potential study will provide data on the abuse potential of Dronabinol Oral Solution (Schedule I) relative to that of Marinol capsules (Schedule III). Dronabinol Oral Solution needs to be tested 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.

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 the 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.

CSS is available to evaluate a protocol for the human abuse potential study prior to its initiation, if desired.

Reference ID: 3217957

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/s/

KATHERINE R BONSON
11/16/2012

SILVIA N CALDERON
11/16/2012

MICHAEL KLEIN
11/16/2012