DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205525

NDA APPROVAL

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

Dear Mr. Sherman:

Please refer to your New Drug Application (NDA) dated June 1, 2015, received June 1, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Syndros (dronabinol oral solution), 5 mg/mL.

We acknowledge receipt of your major amendment dated March 10, 2016, which extended the goal date by three months.

This new drug application provides for the use of Syndros (dronabinol oral solution) for 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.

CONTROLLED SUBSTANCE SCHEDULING

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on June 1, 2015, and March 2, 2016, you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert, the instructions for use and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of Syndros in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 23, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 205525**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pediatric AIDS patients birth to 17 years of age because necessary studies are highly impracticable. This is because the number of children age 0 to 17 years old with AIDS is very small.

We are deferring submission of your pediatric studies for ages birth to 17 years in pediatric cancer patients for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

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 three-month neonatal rat toxicity study with Syndros (dronabinol oral solution).

Final Protocol Submission:	08/2016
Study Completion:	11/2016
Final Report Submission:	01/2017

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.

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

3044-3 Deferred study 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.

Final Protocol Submission:	09/2018
Study Completion:	11/2018
Final Report Submission:	11/2021

3044-4 Deferred pediatric study under PREA to evaluate the tolerability and efficacy of Syndros (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.

Final Protocol Submission:	07/2019
Study Completion:	09/2022
Final Report Submission:	03/2023

Submit the protocols to your IND 075228, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of a potential for neurocognitive impairment following prenatal exposure to delta-9-THC (dronabinol).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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

The timetable you submitted on June 23, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2016
Study Completion:	10/2017
Final Report Submission:	07/2018

Submit the protocol(s) to your IND 075228, with a cross-reference letter to this NDA 205525. Submit all final report(s) to your NDA 205525. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii) . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Content of Labeling
Patient Labeling (PPI)
Instructions for Use
Carton and Container Labeling

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

/s/

ANDREW E MULBERG
07/01/2016