LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.
700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

JOHN A. GILBERT, JR.

Direct Dial (202) 737-4293
JGilbert@hpm.com

January 3, 2011

VIA ELECTRONIC AND OVERNIGHT DELIVERY

Drug Enforcement Administration
Attention: DEA Federal Register Representative/ODL
8701 Morrissette Drive
Springfield, Virginia 22152

RE: Docket No. DEA-344P; DEA-2010-0023
Comments on Notice of Proposed Rulemaking: Listing of Approved Drug Products Containing Dronabinol in Schedule III

Dear Sir or Madam:

On behalf of INSYS Therapeutics, Inc. the undersigned hereby respectfully submits this comment to the Drug Enforcement Administration's ("DEA's") Notice of Proposed Rulemaking ("NPR") on the "Listing of Approved Drug Products Containing Dronabinol in Schedule III."

The DEA is proposing to expand the schedule III listing at 21 C.F.R. § 1308.13 for dronabinol so that certain generics of different formulations are also included in the listing. Specifically, DEA is proposing to include formulations containing naturally-derived dronabinol and hard gelatin capsules in the listing for schedule III. The rule would re-schedule from schedule I to III those approved generic drug products that contain dronabinol in a natural or other form that reference the branded drug. In support of its position, the DEA relies on two recommendations by the Department of Health and Human Services ("HHS"), dated March 17, 2010 and June 1, 2010, that a schedule III listing for FDA-approved generic products containing naturally-derived dronabinol in a hard gelatin capsule is appropriate. *See* 75 Fed. Reg. at 67,057 (Nov. 1, 2010).

Although DEA is bound by HHS's findings concerning scientific and medical matters (21 U.S.C. § 811(b)), DEA must make the ultimate decision as to the abuse potential of a drug, considering all of the eight factors required for determining in which schedule to place a drug. *Id.* DEA's current proposal to expand the definition of the current scheduling of dronabinol should only be made after DEA has considered all of information on the potential for abuse of different formulations of dronabinol.

Based on a review of the proposed rule and HHS's submission to the DEA, INSYS Therapeutics, Inc. has identified two other areas which should be reviewed and addressed before DEA makes a final decision on expanding the schedule III classification of dronabinol.

(1) Diversion and Abuse Potential of Cultivating Marijuana.

One of the eight factors that must be considered under the Controlled Substances Act ("CSA"), 21 U.S.C. § 811(c), for scheduling a substance is the "actual or relative potential for abuse." The DEA must also consider the history and pattern of abuse and all factors that may be relevant to the abuse potential of a substance.

The HHS's analysis of naturally-derived dronabinol states that the "source of the dronabinol, whether naturally-derived or synthetic, does not alter the abuse potential for the substance." (June 1, 2010 Letter from Howard K. Koh, Assistant Secretary for Health, DHHS, to the Honorable Michele Leonhart, Acting Administrator, DEA, attachment thereto at 4). This statement presents the obvious conclusion that if the resulting molecule is identical from either a chemical synthesis or an extraction of the plant material, the abuse potential of the molecule would be identical. The HHS's analysis of products that contain dronabinol in a natural versus synthetic form does not indicate or otherwise demonstrate whether the drug sponsor's production and distribution practices for the unfinished form of naturally-derived dronabinol are not otherwise susceptible to diversion and abuse. Similarly, HHS did not address whether the Agency had an opinion on whether the generic version containing natural dronabinol has a lower or higher potential of abuse or diversion given the different cultivation and manufacturing process of the active pharmaceutical ingredient ("API") from naturally-derived dronabinol or whether HHS has received, reviewed or considered any data on this issue.

The HHS analysis also does not consider the abuse potential in terms of the need to grow and cultivate substantial crops of marijuana in the United States. Given that the active ingredient in naturally-derived dronabinol is not derived from a laboratory

comparable to the synthetic version, there is no indication that HHS considered whether the approval and use of the naturally-derived product would increase diversion or abuse potential because more of the natural form of the product (delta-9-THC) would be cultivated or grown as marijuana, and then harvested and extracted to manufacture the naturally-derived product.

Marinol® and other generics derived from synthetic THC involve a laboratory process where the API is synthesized rather than extracted from a plant. The manufacture is complex and expensive because of the "numerous steps needed for purification." Marijuana and Medicine: Assessing the Science Base, Institute of Medicine, pgs. 202-203 (1999). This is likely one reason why there appears to be no published reports of clandestine attempts to manufacture synthetic delta-9-THC. On the other hand, the illicit growing and distribution of marijuana has been a long-standing problem in the United States. The clandestine manufacture of marijuana is similarly a serious concern in the United States. *See, e.g.*, 14,500 Marijuana Plants Seized in Pike National Forest Near Deckers, *www.justice.gov/dea/pubs/states/newsrel/2009; see also* The National Drug Threat Assessment 2009, *www.justice.gov/ndic/pubs31/31379/marijuan.html*. For this reason, DEA initiated the Domestic Cannabis Eradication/Suppression Program (DCE/SP) to halt the spread of cannabis cultivation in the United States. In 2009, DEA provided additional resources to support the 119 state and local law enforcement agencies that actively participate in the program. *See www.justice.gov/dea/prgrams/marijuana.html*.

DEA should consider that growing and cultivation of marijuana plants in the United States for use in naturally-derived dronabinol products could potentially increase the diversion and abuse of marijuana. It has been a longstanding policy of the United States to disfavor domestic cultivation of narcotic raw materials because of concerns about the abuse potential from the farming of this material. The DEA has never approved a manufacturer in the United States to grow and cultivate narcotic raw materials. All narcotic raw materials for manufacturing of important pain medicines must be imported from countries with experience and technology in cultivating the plant material. Similarly, DEA should consider these same policy objectives in regard to the impact of authorizing the cultivation and growth of marijuana for production of generic drugs containing natural plant material.

(2) Hard Gelatin Capsules.

We are aware that FDA is generally concerned about the potential "leak rate" for hard gelatin capsules. The FDA appears to have issues with the liquid filled hard gelatin capsule technology, including ensuring that the capsule sealing process must yield a 100

percent leak-free capsule. This issue is clearly a factor that FDA must consider in evaluating whether to approve a generic form of Marinol®. DEA should ensure that this issue has been addressed by FDA and that such issue would not raise concerns about the abuse potential of a hard gelatin formulation.

In conclusion, the DEA is charged by Congress with the enforcement of controlled substances laws and to protect the public against the potential for diversion and abuse of such substances. Because it is DEA's and not HHS's ultimate determination concerning the scheduling of controlled substances, DEA should, consistent with its duty to protect the public from diversion and abuse, ensure that its review of the basis for rescheduling dronabinol fully considers the potential for abuse of a naturally-derived formulation and/or a hard gelatin capsule.

Respectfully submitted,

John A. Gilbert, Jr.