DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

JUN - 1 2010

The Honorable Michele Leonhart
Acting Administrator
Drug Enforcement Administration
Lincoln Place – West
700 Army Navy Drive, Room 12060
Arlington, VA 22202

Dear Ms. Leonhart:

Pursuant to the Controlled Substances Act [CSA, 21 U.S.C. 811 (b), (c), and (f)], the Department of Health and Human Services is recommending that FDA-approved drug products containing naturally-derived dronabinol in sesame oil in a gelatin capsule be rescheduled to Schedule III of the CSA. As a result of this recommendation, drug products that are approved by the FDA under section 505(j) of the Food, Drug and Cosmetic Act (21 USC 355) (commonly referred to as generic drugs) containing naturally-derived dronabinol in sesame oil in a gelatin capsule that cite Marinol as the reference listed drug (RLD) will be controlled in Schedule III of the CSA.

Marinol is a Schedule III, FDA-approved drug product containing synthetic dronabinol dissolved in sesame oil and encapsulated in soft gelatin capsules (2.5 mg, 5 mg, and 10 mg per dosage unit). Dronabinol is also known as delta^9-tetrahydrocannabinol and delta^9-THC. The approval of other Abbreviated New Drug Applications (ANDAs) for generic drug products that reference Marinol, including several that contain synthetic and naturally-derived dronabinol, are pending at FDA.

FDA-approved generic products that reference Marinol, as well as drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule, have a similar potential for abuse as Marinol.

FDA and the National Institute on Drug Abuse have also considered the abuse potential and dependence producing characteristics of naturally-derived dronabinol in sesame oil in a gelatin capsule. After reviewing the available information, the agencies conclude that drug products approved for marketing by FDA that contain naturally-derived dronabinol in sesame oil in a gelatin capsule should be rescheduled to Schedule III of the CSA. Enclosed is a document prepared by FDA's Controlled Substance Staff that is the basis for the recommendation.

Should you have any questions regarding this recommendation, please contact Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff, Center for Drug Evaluation and Research at (301) 796-5402.

Sincerely yours,

Howard K. Koh, M.D., M.P.H.
Assistant Secretary for Health

Enclosure

BASIS FOR THE RECOMMENDATION TO RESCHEDULE FDA-APPROVED DRUG PRODUCTS CONTAINING NATURALLY-DERIVED DRONABINOL IN SESAME OIL IN A GELATIN CAPSULE TO SCHEDULE III OF THE CONTROLLED SUBSTANCES ACT

I. INTRODUCTION

The Food and Drug Administration (FDA) is recommending that FDA-approved generic drug products that reference Marinol and contain naturally-derived dronabinol in sesame oil and encapsulated in a gelatin capsule be rescheduled to Schedule III of the Controlled Substances Act (CSA). As a result of this recommendation, drug products that are approved by the FDA under section 505(j) of the Food, Drug and Cosmetic Act (21 USC 355), commonly referred to as generic drugs, containing naturally-derived dronabinol in sesame oil in a gelatin capsule that cite Marinol as the reference listed drug (RLD) will be controlled in Schedule III of CSA. As described in Section II. Marinol is a Schedule III, FDA-approved drug product containing synthetic dronabinol dissolved in sesame oil and encapsulated in soft gelatin capsules (2.5 mg, 5 mg, and 10 mg per dosage unit). Dronabinol is also known as delta^{9}-tetrahydrocannabinol and delta^{9}-THC. Previously, FDA approved a generic drug product that contains synthetic dronabinol in sesame oil, encapsulated in a soft gelatin capsule that was controlled in Schedule III of the CSA upon FDA approval.

In 2006, the Drug Enforcement Administration (DEA) received a petition on behalf of Cobalt Pharmaceuticals, Inc.,[1] a drug company that is developing a generic drug product that references Marinol, requesting that the product be placed into Schedule III, similar to that of Marinol. This drug product contains naturally-derived dronabinol dissolved in sesame oil and encapsulated in a gelatin capsule at three dosage strengths (2.5 mg, 5 mg, and 10 mg per dosage unit). In the petition, the drug company asserts that their generic drug product that references Marinol has similar chemical properties, composition, and therapeutic value as those of Marinol. DEA subsequently requested in 2007 that the Department of Health and Human Services (HHS) conduct a medical and scientific evaluation of the petition.

Pursuant to 21 U.S.C. § 811(b) of the CSA, the Secretary of the HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the CSA. Following consideration of the eight factors, the Secretary must make three findings and a recommendation for scheduling a substance or drug. The eight factors are:

1. The drug's actual or relative potential for abuse;
2. Scientific evidence of the drug's pharmacological effects, if known;
3. The state of current scientific knowledge regarding the drug or other substance;
4. The drug's history and current pattern of abuse;

[1] Cobalt was acquired by Impax Laboratories, Inc. in December 2009.

5. The scope, duration, and significance of abuse;
6. What, if any, risk there is to the public health;
7. The drug's psychic or physiological dependence liability; and
8. Whether the substance is an immediate precursor of a substance already controlled.

The three required findings relate to the substance's abuse potential, legitimate medical use, and safety or dependence potential. 21 U.S.C. § 812(b).

Administrative responsibilities for evaluating a substance for control under the CSA are performed for HHS by FDA, with the concurrence of the National Institute on Drug Abuse (NIDA) [Memorandum of Understanding, 50 Fed. Reg. 9518, 9518-20 (Mar. 8, 1985)].

This evaluation discusses the scientific and medical information relative to each of the eight factors, presents findings in the three required areas, and includes a recommendation regarding scheduling. In this document, FDA recommends that FDA-approved generic drug products that reference Marinol, and thus are chemically, pharmacologically, and pharmacokinetically similar, and that contain naturally-derived dronabinol in sesame oil in a gelatin capsule be controlled in Schedule III of the CSA. Drug products containing natural dronabinol in sesame oil and encapsulated in a gelatin capsule in an FDA-approved product are similar to Marinol with regard to abuse potential. This FDA evaluation focuses only on FDA-approved generic drug products and does not apply to any other preparations, mixtures, compounds, or formulations of dronabinol that are currently in Schedule I of the CSA. Pursuant to 21 U.S.C. 811(c), the eight factors pertaining to the scheduling of FDA-approved generic drug products that reference Marinol are considered below.

II. BACKGROUND

Marinol is a drug product containing synthetic dronabinol dissolved in sesame oil and encapsulated in soft gelatin capsules in dosage units of 2.5 mg, 5 mg and 10 mg. The approved drug product specifications are 95-110% dronabinol (delta^{9}-tetrahydrocannabinol (delta^{9}-THC)) and no more than 2% of the impurity delta^{8}-tetrahydrocannabinol (delta^{8}-THC). Marinol was approved by FDA for marketing on May 31, 1985, for the indication of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Subsequently, on December 22, 1992, Marinol was approved for the indication of treatment of anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS).

Prior to the approval of Marinol, all preparations, mixtures, compounds, and formulations containing dronabinol, including cannabis, were listed in Schedule I of the CSA. Following the approval of Marinol, dronabinol was rescheduled to Schedule II on May 13, 1986 (51 FR 17476). 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."

Subsequently, 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 Marinol in sesame oil supported the finding of a lower abuse potential relative to substances in Schedule II (Sapienza, 2006). During both of these rescheduling actions for Marinol, all other preparations, mixtures, compounds, and formulations of dronabinol, including cannabis, were retained in Schedule I.

On June 27, 2008, an Abbreviated New Drug Application (ANDA) sponsored by Par Pharmaceutical, Inc. (Par), was approved under 505(j) of the Act with Marinol as the RLD. Par's drug product contains synthetic dronabinol in sesame oil, encapsulated in a soft gelatin capsule at doses of 2.5 mg, 5 mg, and 10 mg per dosage unit. Given that the formulation of this generic drug product is similar to that of Marinol, and thus met the description in 21 CFR 1308.13(g)(1), it was controlled in Schedule III of the CSA upon FDA approval.

The approval of other ANDAs for generic drug products that reference Marinol, including several that contain synthetic and naturally-derived dronabinol, are pending at FDA.

During the ANDA approval process, the chemistry-manufacturing-control (CMC) review of the purity of each generic drug product ensures that there is no difference in the active pharmaceutical ingredient (API), dronabinol, contained in Marinol and in the generic drug products that reference Marinol. The ANDA approval process also ensures that the proposed generic product has the same strength, formulation (e.g., sesame oil in a hard or soft gelatin capsule), route of administration, and conditions of use (labeling) as the RLD and that the generic product is bioequivalent to that drug. For each generic drug product containing dronabinol of natural origin, FDA will ensure, prior to approval of the ANDA, that any cannabinoid impurities present do not confer an abuse potential to the generic product that is different from that of the RLD. Thus, the abuse potential of dronabinol in sesame oil in a capsule in FDA-approved generic drug products that reference Marinol will be similar, regardless of whether the API is obtained through synthetic means or is derived from natural cannabis.

III. Evaluating FDA-Approved Generic Drug Products Containing Naturally-Derived Dronabinol that Reference Marinol Under the Eight Factors

This section presents the current scientific and medical information about Marinol and FDA-approved generic drug products that reference Marinol and contain naturally-derived dronabinol in sesame oil in a gelatin capsule under the eight factors required to be evaluated by the CSA.

1. THE DRUG'S ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The first factor the Secretary must consider is the actual or relative potential for abuse of FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol.

The term "abuse" is not defined in the CSA. The following points in determining whether a particular drug or substance has a potential for abuse are suggested by the legislative history of the CSA[2]:

a. Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.
b. There is significant diversion of the drug or substance from legitimate drug channels.
c. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance.
d. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

FDA-approved generic drug products that reference Marinol have the same API (dronabinol) as that found in Marinol, an FDA-approved Schedule III drug product, have similar chemistry, pharmacology and pharmacokinetics, and therefore have similar potentials for abuse. Dronabinol is an agonist at cannabinoid receptors and has a recognized abuse potential (see Factor 2, below). The source of the dronabinol, whether naturally-derived or synthetic, does not alter the abuse potential of the substance. Given these similarities, FDA-approved generic drug products containing naturally-derived dronabinol in sesame oil and encapsulated in a gelatin capsule are expected to be indistinguishable from Marinol in terms of the amounts taken by individuals and the impact on the community resulting from the products' diversion from legitimate drug channels or their use outside of legitimate medical practice.

2. SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECTS, IF KNOWN

The second factor the Secretary must consider is scientific evidence of the pharmacological effects of FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. This section includes a scientific evaluation of the neurochemistry, pharmacology, human and animal

[2] Comprehensive Drug Abuse Prevention and Control Act of 1970. H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.

behavioral effects, and tolerance associated with dronabinol, the API in FDA-approved generic drug products that reference Marinol. The overview presented below relies upon the most current research literature on dronabinol.

A. Neurochemistry and Pharmacology of Dronabinol

Dronabinol is a cannabinoid that can be derived naturally from cannabis as well as by a synthetic chemical process. Dronabinol is considered the major psychoactive cannabinoid constituent of cannabis (Wachtel et al., 2002). The structure and function of dronabinol was first described in 1964 by Gaoni and Mechoulam. Two cannabinoid receptors, CB_1 and CB_2, have been characterized (Piomelli, 2005).

Autoradiographic studies have provided information on the distribution of cannabinoid receptors. CB_1 receptors are found in the basal ganglia, hippocampus and cerebellum of the brain (Howlett et al., 2004) as well as in the immune system. It is believed that the localization of these receptors may explain cannabinoid interference with movement coordination and effects on memory and cognition. Concentration of CB_1 receptors is considerably lower in peripheral tissues than in the central nervous system (Henkerham et al., 1990 and 1992). CB_2 receptors are found primarily in the immune system, predominantly in B lymphocytes and natural killer cells (Bouaboula et al., 1993). It is believed that the CB_2-type receptor is responsible for mediating the immunological effects of cannabinoids (Galiegue et al., 1995). However, CB_2 receptors also have recently been localized in the brain, primarily in the cerebellum and hippocampus (Gong et al., 2006).

Dronabinol displays similar affinity for CB_1 and CB_2 receptors but behaves as a weak agonist for CB_2 receptors, based on inhibition of adenylate cyclase. The identification of synthetic cannabinoid ligands that selectively bind to CB_2 receptors, but do not have the typical dronabinol-like psychoactive properties suggests that the psychotropic effects of cannabinoids are mediated through the activation of CB_1-receptors (Hanus et al., 1999). Naturally-occurring cannabinoid agonists, such as dronabinol and the synthetic cannabinoid agonists such as WIN-55,212-2 and CP-55,940, produce the classic cannabinoid effects of hypothermia, analgesia, hypoactivity and cataplexy, in addition to their psychoactive effects.

B. Central Nervous System Effects

Human Physiological and Psychological Effects

Subjective Effects

The physiological, psychological and behavioral effects of dronabinol vary among individuals. Common responses to cannabinoids, as described by Adams and Martin (1996) and others (Hollister 1986a, 1988a), are listed below:

1) Dizziness, nausea, tachycardia, facial flushing, dry mouth and tremor initially

2) Merriment, happiness and even exhilaration at high doses
3) Disinhibition, relaxation, increased sociability, and talkativeness
4) Enhanced sensory perception, giving rise to increased appreciation of music, art and touch
5) Heightened imagination leading to a subjective sense of increased creativity
6) Time distortions
7) Illusions, delusions and hallucinations, especially at high doses
8) Impaired judgment, reduced co-ordination and ataxia, which can impede driving ability or lead to an increase in risk-taking behavior
9) Emotional lability, incongruity of affect, dysphoria, disorganized thinking, inability to converse logically, agitation, paranoia, confusion, restlessness, anxiety, drowsiness and panic attacks, especially in inexperienced users or in those who have taken a large dose
10) Increased appetite and short-term memory impairment

These subjective responses to cannabinoids are pleasurable to many humans and are associated with drug-seeking and drug-taking (Maldonado, 2002).

Animal behavioral effects

Self-Administration

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative of abuse liability. Generally, a good correlation exists between those drugs that are self-administered by rhesus monkeys and those that are abused by humans (Balster and Bigelow, 2003).

Interestingly, self-administration of hallucinogenic-like drugs, such as cannabinoids, LSD, and mescaline, has been difficult to demonstrate in animals (Yanagita, 1980). However, when it is known that humans voluntarily consume a particular drug (such as cannabis) for its pleasurable effects, the inability to establish self-administration with that drug in animals has no practical importance in the assessment of abuse potential. This is because the animal test is a predictor of human behavioral response in the absence of naturalistic data.

The experimental literature generally reports that animals not previously exposed to cannabinoids will not self-administer cannabinoids unless they have had previous experience with other drugs of abuse. However, when squirrel monkeys are first trained to self-administer intravenous cocaine, they will continue to bar-press at the same rate as when dronabinol is substituted for cocaine, at doses that are comparable to those used by humans who smoke cannabis (Tanda et al., 2000). This effect is blocked by drugs with cannabinoid receptor antagonist properties, such as rimonabant. New studies show that monkeys without a history of any drug exposure can be successfully trained to self-administer dronabinol intravenously (Justinova et al., 2003).

These data demonstrate that under specific pretreatment conditions, an animal model of reinforcement by cannabinoids now exists for future investigations. Rats will self-administer dronabinol when it is applied intracerebroventricularly (i.c.v.), but only at the lowest doses tested (0.01-0.02 μg /infusion) (Braida et al., 2004). This effect is antagonized by rimonabant and by the opioid antagonist naloxone (Braida et al., 2004).

There may be a critical dose-dependent effect,since aversive effects, rather than reinforcing effects, have been described in rats that received high doses of dronabinol (Sanudo-Pena et al., 1997). Rimonabant reversed these aversive effects.

Conditioned Place Preference

Conditioned place preference (CPP) is a less rigorous method than self-administration of determining whether drugs have rewarding properties. In this behavioral test, animals are given the opportunity to spend time in two distinct environments: one where they previously received a drug and one where they received a placebo. If the drug is reinforcing, animals will choose to spend more time in the environment paired with the drug than the one paired with the placebo, when both options are presented simultaneously.

Animals show CPP to dronabinol, but only at the lowest doses tested (0.075-0.75 mg/kg, i.p.) (Braida et al., 2004). This effect is antagonized by rimonabant as well as by naloxone (Braida et al., 2004).

Drug Discrimination Studies

Drug discrimination is a method in which animals indicate whether a test drug produces physical or psychic perceptions similar to those produced by a known drug of abuse. In this test, an animal learns to press one bar when it receives the known drug of abuse and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is like the known drug of abuse.

Animals, including monkeys and rats (Gold et al., 1992), as well as humans (Chait, 1988), can discriminate cannabinoids from other drugs or placebo. Discriminative stimulus effects of dronabinol are pharmacologically specific for cannabinoids (Balster and Prescott, 1992, Barrett et al., 1995, Browne and Weissman, 1981, Wiley et al., 1993, Wiley et al., 1995). Additionally, the major active metabolite of dronabinol, 11-hydroxy-delta^9-THC, also generalizes to the stimulus cue elicited by dronabinol (Browne and Weissman, 1981).

The discriminative stimulus effects of the cannabinoid group appear to provide unique effects because stimulants, hallucinogens, opioids, benzodiazepines, barbiturates, N-methyl d-aspartate (NMDA) antagonists and antipsychotics do not fully substitute for dronabinol.

C. Tolerance to the Effects of Dronabinol

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001). The presence of tolerance does not determine whether a drug has abuse potential, in the absence of other abuse indicators such as reinforcing or rewarding properties.

Tolerance to the psychotomimetic and amnesic effects of dronabinol develops in humans following chronic exposure (D'Souza et al., 2008). Tolerance also develops in humans to the cardiovascular and autonomic changes, decreased intraocular pressure, and sleep alterations induced by dronabinol (Jones et al., 1981). Down-regulation of cannabinoid receptors has been suggested as the mechanism underlying tolerance to the effects of dronabinol (Wu et al., 2008, Rodriguez de Fonseca et al., 1994, Oviedo et al., 1993).

However, in performance tasks, humans have a variable response to chronic use of cannabinoids. In long-term cannabis users, performance on neurocognitive tasks such as perceptual motor control and dual task processing following administration of dronabinol was not reduced compared to moderate cannabis users (Ramaekers et al., 2008). Additionally, reaction times are not altered by administration of dronabinol in long-term cannabis users (Block and Wittenborn, 1985). This may be related to electro-physiological data showing that the ability of dronabinol to increase neuronal firing in the ventral tegmental area (a region known to play a critical role in drug reinforcement and reward) is not reduced following chronic administration of the drug (Wu and French, 2000).

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

The third factor the Secretary must consider is the state of current scientific knowledge regarding FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. Given that the API in these products is dronabinol, this section will discuss the chemistry and human pharmacokinetics of this drug substance.

A. Chemistry

The API in Marinol and currently-approved generic drug products that reference Marinol is dronabinol. Dronabinol is a cannabinoid designated chemically as (6aR-trans)-6a, 7, 8, 10a-tetrahydro-6, 6, 9-trimethyl-3-pentyl-6H-dibenzo [b,d]pyran-1-ol. Dronabinol is a naturally occurring component of Cannabis sativa L. (Marijuana). There is no substantial difference chemically between synthetic dronabinol and naturally-derived dronabinol.

Dronabinol is a light yellow resinous oil that is sticky at room temperature and softens upon refrigeration. Its molecular formula is $C_{21}H_{30}O_2$ and it has a molecular weight of 314.47. Dronabinol is insoluble in water, but is very soluble in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

The dronabinol contained in Marinol and in the generic drug products that reference Marinol is formulated with sesame oil. The three dosage formulations of Marinol contain 2.5, 5 and 10 mg of dronabinol in sesame oil in gelatin capsules. This formulation is intended for oral administration only. It is difficult to separate dronabinol in pure form from sesame oil because these two substances have similar physical and chemical properties. Intravenous use is difficult because an aqueous solution of pure dronabinol cannot be created easily. Additionally, attempts to smoke dronabinol formulated in sesame oil results in an undesirable production of soot and oil ignition, based on the presence of long-chain hydrocarbons in the sesame oil. The ability of sesame oil to catch fire easily is verified by its historical use as a lamp oil (Copley et al., 2005).

B. Human Pharmacokinetics

The human pharmacokinetics of dronabinol in Marinol capsules are described in the drug label. Clinical pharmacology assessment ensures that generic drug products that reference Marinol are bioequivalent to Marinol, thus meeting the requirements for generic drug approval by FDA.

Following single oral doses, dronabinol is almost completely absorbed (90 to 95%). However, after dronabinol absorption, first-pass hepatic elimination from blood leads to a low and variable bioavailability, ranging from 5 to 20 percent. Dronabinol is very lipid soluble, leading to a large apparent volume of distribution (approximately 10 L/kg) and efficient delivery to the brain. The plasma protein binding of dronabinol and its metabolites is approximately 97%.

The pharmacokinetics of dronabinol after single doses (2.5, 5 or 10 mg) and multiple doses (2.5, 5 or 10 mg given twice a day; BID) have been studied in healthy volunteers and are reported in the drug label for Marinol, as shown in Table 3 below:

Table 1: Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol in Healthy Volunteers

	Mean (SD) PK Parameter Values		
BID Dose	**Cmax ng/mL**	**Median Tmax (range), hr**	**AUC (0-12) ng•hr/mL**
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

A slight increase in dose proportionality on mean Cmax and AUC (0-12) of dronabinol was observed with increasing dose over the dose range studied.

The onset of effects after oral administration of dronabinol is 30-90 min, with a peak at approximately 2-3 hours and continuing effects for 4-12 hours (Grotenhermen, 2003; Adams and Martin 1996; Agurell et al. 1984, 1986). Following oral administration of radioactive-labeled dronabinol, plasma levels of dronabinol are low relative to those levels after smoking or intravenous administration. There is inter- and intra-subject variability, even when repeated dosing occurs under controlled conditions.

Cannabinoid metabolism is extensive. Dronabinol is metabolized via microsomal hydroxylation to both active and inactive metabolites (Lemberger et al., 1970, 1972a, 1972b; Agurell et al., 1986; Hollister, 1988a) of which the primary active metabolite is 11-hydroxy-delta^9-THC. This metabolite is approximately equipotent to dronabinol in producing cannabinoid-like subjective effects (Agurell et al., 1986, Lemberger and Rubin, 1975). In addition to 11-hydroxy-delta^9-THC, some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more. The majority of the absorbed dronabinol dose is eliminated in feces, and about 33 percent in urine. Dronabinol enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta^9-THC. The glucuronide is excreted as the major urine metabolite along with about 18 nonconjugated metabolites.

According to the drug label for Marinol, the elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time. The terminal half-life of dronabinol is estimated to range from approximately 20 hours to as long as 10 to 13 days (Hunt and Jones, 1980). However, reported estimates vary as is expected with any slowly cleared substance and because of the use of assays of variable sensitivities.

Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radio-labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces.

Following single-use administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

4. THE DRUG'S HISTORY AND CURRENT PATTERN OF ABUSE

The fourth factor the Secretary must consider is the history and current pattern of abuse of FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. Since generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol are not currently marketed, no information is available regarding their pattern of abuse.

However, approved generic drug products that reference Marinol have the same API (dronabinol) and similar chemistry and pharmacokinetics as Marinol, an FDA-approved Schedule III drug product. Dronabinol is an agonist at cannabinoid receptors and has a known abuse potential in humans (see Factor 2, above).

The eight factor analysis and recommendation for placement of Marinol into Schedule III (HHS, 1998) stated that, "A pattern of abuse of Marinol has not been uncovered. Only sporadic reports of small amount of diversion have been documented. Comparisons of patterns of abuse [between marijuana and Marinol] illustrate that there is considerable abuse of marijuana and virtually none of Marinol. One factor contributing to these few occurrences of diversion and abuse is no doubt the limited general availability of Marinol, worldwide or nationally, relative to that of marijuana." Thus, it is expected that generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule will have a similar pattern of abuse to that of Marinol.

The abuse potential of generic drug products approved pursuant to an ANDA is considered to be similar to the RLD based on equivalent quantities of the API present in the dosage form. Thus, the abuse potential of generic drug products that reference Marinol will be similar regardless of whether the API is naturally-derived or synthetic. Given these similarities, FDA-approved generic drug products that reference Marinol will have a similar pattern of abuse as that of Marinol.

5. THE SCOPE, DURATION AND SIGNIFICANCE OF ABUSE

The fifth factor the Secretary must consider is the scope, duration, and significance of abuse of FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. Since generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol are not currently marketed, no information is available regarding their pattern of abuse.

However, approved generic drug products that reference Marinol have the same API (dronabinol) and similar chemistry and pharmacokinetics as Marinol, an FDA-approved Schedule III drug product. Dronabinol is an agonist at cannabinoid receptors and has a

known abuse potential in humans (see Factor 2, above). Approved ANDAs for generic drug products are considered to be similar in activity to the RLD based on equivalent quantities of the API present in the dosage form.

The eight factor analysis and recommendation for placement of Marinol into Schedule III (HHS, 1998) stated that, "Adverse reaction reports have failed to generate any reports of drug abuse, dependence, withdrawal, overdose (intentional or accidental) or tolerance development" with Marinol. Thus, the abuse potential of FDA-approved generic drug products containing dronabinol and reference Marinol will be similar, regardless of whether the API is naturally-derived or synthetic. Given these similarities, generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol will have a scope, duration, and significance of abuse that is similar to that of Marinol.

6. WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

The sixth factor the Secretary must consider is whether there is any risk to the public health from FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. The public health risks can be assessed by evaluating the AEs and overdose symptoms associated with Marinol, since dronabinol is the API in both Marinol and in generic drug products that reference Marinol.

A. Adverse Events

The adverse events (AEs) associated with the use of Marinol are described in the product label. Central nervous system AEs include euphoria, amnesia, anxiety, confusion, depersonalization, hallucination, paranoia, somnolence and abnormal thinking. Peripheral AEs include asthenia, palpitations, vasodilation, abdominal pain, nausea, vomiting. For purposes of assessing abuse potential, euphoria is the most significant AE. However, the other listed AEs can contribute to medical emergencies when individuals use Marinol for abuse purposes.

B. Overdose

The product label for Marinol states that the signs and symptoms of overdose include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth, tachycardia, memory impairment, mood alteration, urinary retention, decreased motor coordination, lethargy, postural hypotension, and panic and seizure disorders. There is no known antidote for Marinol overdose and the treatment is appropriate supportive care.

Thus, any risk to the public health from FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol will be no different than that of Marinol.

7. The Drug's Psychic or Physiologic Dependence Liability

The seventh factor the Secretary must consider is the psychic or physiologic dependence liability of FDA-approved drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol. Given that the API in these products is dronabinol, the dependence liability of this substance will be discussed in this section.

Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001).

In chronic cannabis users, a withdrawal syndrome has been described that consists of restlessness, irritability, mild agitation, insomnia, sleep EEG disturbances, nausea and cramping that resolve within a few days (Haney et al., 1999). This indicates that cannabis produces physical dependence. Similarly, a review of clinical studies on cannabis discontinuation concluded that cannabis produces a withdrawal syndrome that includes such symptoms as sleep difficulties, strange dreams, decreased appetite, decreased weight, anger, irritability and anxiety (Budney et al., 2004). Based on clinical descriptions, this syndrome appears to be mild compared to classical alcohol and barbiturate withdrawal syndromes, which can include more serious symptoms such as agitation, paranoia, and seizures.

A recent study comparing cannabis and tobacco withdrawal symptoms in humans demonstrated that the magnitude and time course of the two withdrawal syndromes are similar (Vandrey et al., 2005). Lane et al. (1998) describes milder cases of dependence including symptoms that are comparable to those from caffeine withdrawal, including decreased vigor, increased fatigue, sleepiness, headache, and reduced ability to work. The marijuana withdrawal syndrome has been reported in adolescents who were admitted for substance abuse treatment or in individuals who were given marijuana on a daily basis during research conditions.

The production of an overt withdrawal syndrome in animals following chronic dronabinol administration is demonstrated under conditions of natural discontinuation. This may be the result of the slow release of cannabinoids from adipose storage, as well as the presence of the major psychoactive metabolite, 11-hydroxy-delta^9-THC. When investigators demonstrated such a withdrawal syndrome in monkeys following termination of cannabinoid administration, the behaviors included transient aggression, anorexia, biting, irritability, scratching and yawning (Budney et al., 2004). However, in rodents treated subacutely with dronabinol, administration of rimonabant, a drug with cannabinoid antagonist properties, produced pronounced withdrawal symptoms including wet dog shakes (Breivogel et al., 2003).

Therefore, the psychic or physiologic dependence liability of FDA-approved drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol will be no different than that of Marinol.

8. WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED UNDER THE CSA

Generic drug products referencing Marinol approved for marketing by FDA that contain naturally-derived dronabinol in sesame oil in a gelatin capsule contain the same API (dronabinol) as Marinol formulated in sesame oil in a gelatin capsule. Dronabinol is not an immediate precursor of any substance controlled under the CSA, as defined in 21 USC 811 (e).

IV. Findings and Recommendation

After consideration of the eight factors determinative of control of a substance [21 U.S.C. 811(c)], FDA recommends that FDA-approved generic drug products that reference Marinol and that contain naturally-derived dronabinol in sesame oil in a gelatin capsule be controlled in Schedule III of the CSA. The data show that the abuse potential of generic drug products that reference Marinol and contain naturally-derived dronabinol in sesame oil in a gelatin capsule is similar to that of Marinol, a Schedule III drug product. Currently the Schedule III Marinol 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." FDA recommends that the description be revised to the following: "Dronabinol (either synthetic or naturally-derived) in sesame oil and encapsulated in a gelatin capsule in a U.S. Food and Drug Administration approved product." NIDA concurs with this recommendation.

The necessary criteria for placing a substance into Schedule III of the CSA are set forth in 21 U.S.C. 812(b)(1), as follows:

(A) The drug or other substance has a potential for abuse less than the drugs or other substances in Schedule II.

FDA-approved generic drug products that contain naturally-derived dronabinol in sesame oil in a gelatin capsule and reference Marinol have a similar potential for abuse as Marinol, a Schedule III drug product. These generic drug products contain the same Active Pharmaceutical Ingredient (API), have similar chemistry and pharmacokinetics ,and have similar formulations in sesame oil.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

Marinol was initially approved by FDA in 1985. When drug products containing naturally-derived dronabinol in sesame oil and encapsulated in a gelatin capsule that reference Marinol receive FDA approval, they will have a currently accepted medical use in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or psychological dependence and such dependence would be less than the drugs or other substances in Schedule II.

The withdrawal syndrome associated with dronabinol, the API in Marinol, produces symptoms in humans such as restlessness, irritability, mild agitation, anxiety, anger, insomnia, sleep EEG disturbances, nausea, decreased appetite, and decreased weight. Since a withdrawal syndrome is indicative of physical dependence, it is reasonable to conclude that generic drug products that contain naturally-derived dronabinol will also produce physical dependence.

FDA therefore recommends that FDA-approved generic drug products that reference Marinol and contain naturally-derived dronabinol in sesame oil in a gelatin capsule be controlled in Schedule III of the CSA. NIDA concurs with this recommendation.

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