

## **The Role of the Physician in “Medical” Marijuana**

President’s Action Committee on Medical Marijuana of the American Society of Addiction Medicine. Members of the committee:

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Based on a literature review, consensus discussions, and a field review, the Action Committee developed a series of findings, conclusions and recommendations regarding the therapeutic value of smoked marijuana and the role of physicians in the prescribing of marijuana for medicinal purposes.

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## ABSTRACT

**Objectives:** Research into the therapeutic potential of cannabis and cannabinoids has lagged behind that of other modern medications. The recent discovery and elucidation of the endocannabinoid receptor system, coupled with improvements in technology and new research tools, has facilitated analytical, pharmacological, and other preclinical research. The conundrum in many states is that liberal cannabis distribution to patients with various medical conditions occurs in a setting where little scientific evidence exists to guide this process in a rational, ethical manner to protect patient health and safety. The purpose of this review is to examine the circumstances that led to this situation and explore the scientific issues involved in moving toward a resolution. It also sets out recommendations to assist physicians in coping with these issues and proposes policy recommendations for consideration that, if adopted, could reduce the potential for more problems in the future.

**Results:** Review findings indicate that in order to think clearly about “medical marijuana,” one must distinguish first between 1) the therapeutic potentials of specific chemicals found in marijuana that are delivered in controlled doses by nontoxic delivery systems, and 2) smoked marijuana. Second, one must consider the drug approval process in the context of public health, not just for medical marijuana but also for all medicines and especially for controlled substances. Controlled substances are drugs that have recognized abuse potential. Marijuana is high on that list because it is widely abused and a major cause of drug dependence in the United States and around the world. When physicians recommend use of scheduled substances, they must exercise great care. The current pattern of “medical marijuana” use in the United States is far from that standard.

**Conclusions:** All cannabis-based and cannabinoid medications should be subjected to the rigorous scrutiny of the Federal Food and Drug Administration (FDA) regulatory process. This process provides important protections for patients, making medications available only when they: 1) are standardized by identity, purity, potency and quality; 2) are accompanied by adequate directions for use in the approved medical indication; and 3) have risk/benefit profiles that have been defined in well-controlled clinical trials.

**Key Words:** cannabis, cannabinoid medication, medical marijuana

## Executive Summary

Research into the therapeutic potential of cannabis and cannabinoids has lagged behind that of other modern medications. The recent discovery and elucidation of the endocannabinoid receptor system, coupled with improvements in technology and new research tools, has facilitated analytical, pharmacological, and other preclinical research. Clinical research is also increasing, although only a small number of controlled studies meeting modern scientific standards have been published.

All cannabis-based and cannabinoid medications should be subjected to the rigorous scrutiny of the Federal Food and Drug Administration (FDA)<sup>1</sup> regulatory process. This process provides important protections for patients, making medications available only when they: 1) are standardized by identity, purity, potency and quality; 2) are accompanied by adequate directions for use in the approved medical indication; and 3) have risk/benefit profiles that have been defined in well-controlled clinical trials. The FDA has set forth the criteria that must be met if a botanically-based medication is to achieve marketing approval through this process.

All major medical organizations support the FDA approval process. Both the American Medical Association (AMA) and the American College of Physicians (ACP) have rejected the use of state legislative enactments to determine whether a medication should be made available to patients. The Institute of Medicine has also rejected this approach and has called for further research into the development of nonsmoked, reliable delivery systems for cannabis-derived and cannabinoid medications. Rigorous research is needed better to understand the significance of different cannabinoid formulations and ratios, methods of administration, and dose-response relationships. Cannabis has a range of effects, some of which may be disturbing to patients with serious medical conditions, adversely impact their cognitive skills, or impair their lung function. Such effects should be better understood, particularly in the context of chronic medical use.

“Medical marijuana,” currently distributed pursuant to state legislation, does not accord with critically important aspects of the modern scientific model. It lacks quality control and standardization; can be contaminated with pesticides and microbes; and does not assure patients a reliable and reproducible dose. Increased cannabis potency heightens the risk of adverse events, especially among cannabis-naïve patients, as well as the dangers of dependence and addiction. There are no effective risk management measures to prevent diversion and abuse, especially by adolescents.

The practice of medicine must be evidence-based; all medical interventions should be justified by high-quality data. Despite the paucity of rigorous scientific data, dispensaries are now distributing cannabis and cannabis products to large numbers of

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<sup>1</sup> Some individuals criticize the FDA as an imperfect, flawed system, but its process is the standard for medication approval in the United States. There is no rationale for carving out large scale exceptions to this review process. Any rationale offered loses currency when one considers the potential harm associated with increasing the availability of a substance with a high abuse liability.

individuals. Yet physicians, who are the gatekeepers of this process under state law, have inadequate information on which to base their judgment if they choose to discuss cannabis as a treatment option with their patients. Physicians should carefully consider their ethical and professional responsibilities before issuing a cannabis recommendation to a patient. A physician should not advise a patient to seek a treatment option about which the physician has inadequate information regarding composition, dose, side effects, or appropriate therapeutic targets and patient populations.

## Introduction

During the past 40 years, popular interest in the therapeutic potential of cannabis has significantly increased, propagated by widespread media attention. Because cannabinoid research poses special challenges, data from such research have accumulated slowly and only recently have gained substantial attention within the scientific and medical communities. The conundrum in many states is: liberal cannabis distribution to patients with various medical conditions; little scientific evidence exists to guide this process in a rational, ethical manner which ensures patient health and safety. This report will examine the circumstances that led to this situation and explore the scientific issues involved in moving toward a resolution. It will also set out recommendations to assist physicians in coping with these issues and propose policy recommendations for consideration that are intended to reduce the potential for more problems in the future.

## Modern History of Cannabis in Medicine

In the early part of the 19<sup>th</sup> century, the European medical community became aware of the therapeutic potential of cannabis-based medications. Dr. William O'Shaughnessy, an Irish physician, conducted clinical and nonclinical work in India with cannabis preparations and upon his return to England, the results of his studies became widely known. Across Europe and North America interest increased in the therapeutic potential of these materials. (O'Shaughnessy WB, 1973) Pharmacists and early pharmaceutical companies (Hamilton HC, Lescohier AW & Perkins RA, 1913) developed oral cannabis extracts and tinctures<sup>2</sup> for various medical conditions. These cannabis preparations were unstable and unreliable, however, because unlike opiates, cannabinoids are lipid-, rather than water-soluble, and sensitive to degradation by heat and light (Garrett ER, Hunt CA, 1974). Because of these characteristics, and the limited technology available at the time, the active ingredients in cannabis preparations were unknown, the preparations lacked standardization, and patient response was variable (Walton RP, 1928).

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<sup>2</sup> Historically, cannabis was used for therapeutic purposes primarily in the form of teas, extracts, tinctures (grains of hemp/hashish resin dissolved in alcohol)—**not in smoked form**. Only in rare cases, involving respiratory conditions was cannabis inhaled. In the 1800s, the composition of this resin would have been about half THC and CBD (of its primary cannabinoids). (Russo EB, 2007). See discussion below.

Reports often blame the enactment of the federal Marihuana Tax Act of 1937, which imposed administrative limitations on the prescription of cannabis preparations,<sup>3</sup> for the contraction in the use of marijuana in medicine. The main reasons for this disappearance were the variable potency of cannabis extracts, the erratic and unpredictable individual responses, the introduction of synthetic and more stable pharmaceutical substitutes such as aspirin, chloral hydrate and barbiturates, and the recognition of important adverse effects such as anxiety and cognitive impairment (Fankhauser M, 2002). Accordingly, cannabis preparations gradually fell out of use by the medical profession.<sup>4</sup> As one prominent physician in 1938 noted (Walton RP, 1938)<sup>5</sup>:

The therapeutic application of Cannabis is more a matter of history than of present-day practice. Synthetic analgesics and hypnotics have almost entirely displaced these preparations from their original field of application. The newer synthetics are more effective and reliable and, in addition, have been more intensively exploited by commercial interests...The drug has certain remarkable properties and **if its chemical structure were determined and synthetic variations developed**, some of these might prove to be particularly valuable, both as therapeutic agents and as experimental tools (Walton RP, 1938).

Walton's predictions today remain both hopeful and elusive.

Because of the technological challenges involved in cannabinoid formulation and research, it was not until 1964 that the primary psychoactive ingredient in cannabis, delta-9-tetrahydrocannabinol (THC), was identified and synthesized (Mechoulam R & Gaoni Y, 1965). Coincidentally, popular interest in smoked cannabis began to increase significantly. A number of individuals reported that smoking cannabis for recreational purposes seemed to alleviate some of their medical symptoms. Interest grew in finding therapeutic uses for smoked cannabis. More advanced technology in the 1800s and early 1900s might have made a range of cannabinoid medications—similar to that of modern opiates—available, and cannabis smoking might have been relegated to the realm of non-dependent, non-

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<sup>3</sup> The AMA Committee on Legislative Activities expressed concern about the negative impact that the Act would have on the availability of cannabis preparations but acknowledged that such preparations were little used:

“Cannabis at the present time is slightly used for medicinal purposes, but it would seem worthwhile to maintain its status as a medicinal agent for such purposes as it now has. **There is a possibility that a re-study of the drug by modern means may show other advantages to be derived from its medicinal use.**”

<sup>4</sup> A similar situation occurred in the treatment of cancer chemotherapy-induced nausea and vomiting. In the 1970s and 1980s, there was considerable interest in using smoked cannabis and oral THC for these conditions, since existing treatments were inadequate for control of emesis. A number of state departments of health conducted open label studies comparing smoked marijuana, oral THC, and existing antiemetics. Following the development of more effective antiemetic agents such as the 5-HT<sub>3</sub> receptor antagonists interest in using oral THC and smoked cannabis to prevent acute vomiting waned. (Council on Scientific Affairs Report 6, 2001).

<sup>5</sup> At about that time, Dr. Walton was Professor and Head of the Department of Pharmacology and Therapeutics, Medical College of South Carolina, Charleston, S.C., and wrote and published on cannabis in 1938.

medical use for pleasure (McCarberg WH & Barkin RL, 2007).<sup>6</sup> Thus, the “lag” in the technological capabilities of modern science probably contributed to the controversy of “medical marijuana.” That technology has now arrived, and the era of modern cannabinoid medication development is well on its way.

### **The Basis for Cannabinoid Therapeutics**

Momentum for developing cannabinoid medications gained force only after the discovery of endocannabinoid receptors (Munro S, Thomas KL, & Abu-Shaar M, 1993; Howlett AC, 1995) and the brain’s endogenous cannabinoid ligands in the late 1980s and early 1990s (Devane WA, Hanus L, Breuer A et al, 1992). These monumental discoveries, parallel in their basic framework to the discovery of the brain’s endogenous morphine-like neural system (the endorphins), transformed the focus of research from marijuana to the brain itself. These discoveries marked the dawn of cannabinoid neuroscience.

We now understand that an extensive system of nerves within the brain communicate with each other using the same basic chemistry found in marijuana. While we are only beginning to unravel the role the endocannabinoid system plays in overall brain function, Raphael Mechoulam has declared that “The cannabinoid receptors are found in higher concentrations than any other receptor in the brain... and the endocannabinoid system acts essentially in just about every physiological system that people have looked into, so it appears to be a very central system” (Brown D, 2005-2006).

Cannabinoid type 1 (CB1) receptors are distributed throughout the brain, where they are concentrated in the hippocampus, amygdala, basal ganglia, cerebellum, nucleus accumbens and cortex (anterior > posterior). Cannabinoid type 2 (CB2) receptors are generally located peripherally (Herkenham M, Lynn AB, Little MD, et al, 1990). Tonic activity within the endocannabinoid system is continuously modulating a huge variety of physiological and brain functions, including short-term memory, learning, appetite, anxiety/fear, pain, and spontaneous motor activity.

Two aspects of the endocannabinoid system are important from the addiction medicine perspective. First, CB1 receptors and endocannabinoid ligands are heavily concentrated in the nucleus accumbens – the final common pathway activated by drugs of addiction in the Reward Center. Frequent flooding of these receptors by the ingestion of exogenous cannabinoids is in part responsible for the development of dependence (Budney A, Hughes JR, Moore BA, et al, 2004). Also contributing to withdrawal symptoms is the downregulation of cannabinoid receptors by up to 60% in response to exogenous cannabinoids (Romera J, 1997).

CB1 knockout mice, which have virtually no cannabinoid activity in the central nervous system (CNS), have been used to assess the overall role of our endocannabinoid

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<sup>6</sup> “Unlike cannabis, the medicinal and recreational forms of opium were clearly distinct. Had medical technology been advanced enough at that time to allow cannabinoids to be identified, formulated, and delivered, *the “medical marijuana” movement would probably not have occurred.* As with the opium poppy, prescription cannabinoid medications and crude herbal cannabis would have been used in very different venues.”

system. Without a functioning cannabinoid system due to a genetically induced lack of CB1 receptors, knockout mice demonstrate increased memories (Marsicano G, Wotjak CT, Azad SC, et al, 2002), decreased extinction of aversive memories, failure to self-administer morphine and a significantly increased mortality from a wide variety of causes (Chhatwal JP, Davis M, et al, 2005).

THC and similar molecules in marijuana are able to affect the brain only because they mimic our natural neurotransmitters, flooding receptor sites with stimulation. All the cannabinoid-based areas of the brain are subsequently activated beyond normal physiological levels. This is generally enjoyable for most people, but not without consequences for many. Smoking marijuana essentially reaches into the brain and increases the activity of one specific subset of neuronal activity – like turning up a rheostat that controls the brain’s endocannabinoid activity.

The question of whether there is medicinal value in stimulating, or reducing, activity in cannabinoid-based portions of the brain depends on three things:

1. Specific areas of the brain where cannabinoid chemistry is concentrated and the functions served by these areas;
2. The specific disease and symptoms being treated; and
3. Side effects produced by the treatment - essentially a “medical cost/benefit analysis”.

In addition there are also cannabinoid receptors (CB2) found throughout the body, on nerves, blood cells, on organs, and throughout all stages of embryonic development. The potential for cannabinoid therapeutics must also look at the direct impact of stimulating or antagonizing these receptors as well.

The potential value of any cannabinoid medication depends on modifying physiologic functions that are naturally controlled by our body’s internal cannabinoid system. Given all the functions that are modulated by endocannabinoid chemistry, it is likely that either stimulating or blocking portions of this ubiquitous neuronal subsystem has the potential for relieving the suffering caused by disease. The basic neuroscience of our endocannabinoid system thus provides the American Society of Addiction Medicine’s (ASAM) perspective on the most effective framework for medicalizing cannabinoid therapeutics.

- A. ASAM recognizes that a role has been established for the body’s natural cannabinoid chemistry in regulating many facets of memory, pain, emotions, appetites, motor activity, digestion, attention, higher order executive functions, reward/addiction, the immune system, and reproductive activity.
- B. Multiple illnesses affecting these functions, such as dementia, chronic pain, anxiety, post traumatic shock disorder (PTSD), wasting syndrome, spasticity, diarrhea, irritable bowel syndrome, the nausea/vomiting of chemotherapy and applications still being explored in research labs, are likely to benefit from medications based on our body’s inherent cannabinoid chemistry.

- C. The new cannabinoid medications being developed will range from ones that directly stimulate cannabinoid receptors to ones that prolong the effect of our natural cannabinoid chemistry (similar to how most antidepressants work) to ones that block the receptors in order to reduce the activity of our cannabinoid system. Medications are also being developed that can target only portions of our cannabinoid system without affecting the whole system (for example, reducing pain in the body without affecting the brain) (Ibrahim MM, Deng H, et al, 2003; Quartilho A, Mata HP, et al, 2003).

The exciting discoveries summarized above regarding the endocannabinoid system have stimulated preclinical research:

“This evolution has followed the same principles as the evolution of drug therapy in general. The direction has been away from crude substances of variable composition, stability, and potency, toward the development of progressively more selectively active pure compounds that permit dosage that is more precise and reduced risk of unwanted side effects. (Varvel SA, Wise LE, et al, 2007) <sup>25</sup>”

After a delay of over a century, we are now on the cusp of a new era in which many cannabinoid products could become part of the physician’s armamentarium. A number of cannabinoid products are already in development. Several are plant-derived (Sativex®, Cannador®); others are synthetic analogues (Chatwal JP, 2005) or ligands at the CB2 rather than the CB1 receptor (Marsicano G, Wotjak, et al, 2002; Chhatwal JP, David M, Maguschak KA, et al, 2005; Varvel SA, Wise LE, et al, 2007); still others involve new delivery systems for THC. It will take time for this research to evolve into a range of prescription medications. The duration and complexity of this development process is, however, necessary to ensure that a product’s pharmacology and risk/benefit profile are adequately understood and such preparations can meet FDA standards of consistency, safety and efficacy before the product is distributed to patients.

### **“Medical Marijuana” in the United States**

Fifteen states and the District of Columbia have currently enacted laws that permit the use of cannabis for medical use. Some of the laws have been passed by popular vote through the initiative process; state legislative bodies have promulgated a few. The first of these laws passed in 1996. After having failed for several years to obtain a legislative enactment, cannabis advocates took the issue to the people of California through the initiative process.<sup>7</sup> In most of these states, individual patients and/or their designated

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<sup>7</sup> There were several “medical marijuana” bills introduced into the California legislature, beginning in 1994, e.g., SB 1364, AB 2933, AB 1529, AB 2120, but they either did not pass or were vetoed by the Governor. Coincidentally, these bills followed immediately on the heels of the final disposition of a petition filed by the National Organization for the Reform of Marijuana Laws (NORML), which was filed in 1972 shortly after



caregivers may cultivate cannabis for medical purposes. Some states place limits on the medical conditions that can qualify for legal protection, (e.g., Washington, New Jersey, New Mexico). A few permit the distribution of cannabis by certain types of dispensaries, (e.g., Rhode Island, New Jersey, and New Mexico). Without exception, all of the state laws make physicians the “gatekeepers,” that is, a patient cannot qualify to use cannabis for medical purposes unless a physician has “recommended” the use of cannabis for that person.<sup>8</sup>

As a general rule, these laws do not create new “rights” under state law; rather, they allow a patient (and designated caregivers) to raise his/her personal medical use/cultivation as an affirmative defense if the individual is arrested and charged with violation of certain state criminal laws pertaining to cannabis.<sup>9</sup>

In the first few years following the enactment of the first “medical marijuana” laws, individual patients and their designated caregivers primarily conducted cultivation. Accordingly, the laws had limited application, and research might have been able to provide important data before widespread use occurred. Now, however, the situation has changed dramatically and dispensaries have proliferated at a rapid rate. Many physicians have opened practices based exclusively on issuing cannabis recommendations (see further discussion below). As a result, thousands of persons, with diverse medical conditions (and/or non-medical reasons), are using cannabis, despite the fact that research has not kept (and cannot keep) pace with such rapidly expanding use for the myriad of conditions that cannabis is reported to treat.

## Reports from Expert Bodies

The early “medical marijuana” initiatives garnered widespread media coverage, public interest, and controversy. As a result, a number of expert bodies examined the data relating to the therapeutic potential of cannabis and cannabinoids.

### National Institutes of Health

In 1997, the National Institutes of Health (NIH) hosted a workshop at which medical experts discussed the potential medical uses of smoked cannabis. This group reviewed the

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Congress placed marijuana in Schedule I of the Controlled Substances Act in 1970. NORML initially sought to remove marijuana entirely from the CSA or, alternatively, place marijuana in Schedule V, *NORML v. Ingersoll*, 497 F.2d 654 (D.C. Cir. 1974), but agreed that US treaty obligations did not permit that course of action for cannabis and cannabis resin. *NORML v. DEA*, 559 F.2d 735 (D.C. Cir. 1977) fn. 43. Subsequently, NORML sought to move marijuana to Schedule II. That petition was denied by DEA and, after 22 years of litigation, the DEA denial was upheld by the federal courts. *ACT v. DEA*, 15 F. 3d 1131 (D.C. Cir. 1994).

<sup>8</sup> Since 1) no marijuana-based product has been approved by the FDA, and 2) marijuana is a Schedule I substance under federal law, a physician cannot prescribe, nor can a pharmacist dispense, such a product. Instead, physicians may “recommend” the medical use of cannabis to a specific patient. In Michigan, for example, a physician must certify that the patient is likely to receive medical benefit from the use of cannabis.

<sup>9</sup> For example, the California Supreme Court has ruled that California’s laws confer only a limited immunity which “operates by decriminalizing conduct that otherwise would be criminal.” *People v. Mower* 28 Cal.4<sup>th</sup> 457, 472; 122 Cal.Rptr.2d 326 (2002).

literature and conducted hearings relating to the therapeutic uses of cannabis to treat conditions including: analgesia, neurological and movement disorders, nausea and vomiting associated with cancer chemotherapy, glaucoma, and appetite stimulation/cachexia (National Institutes of Health, 1997). For a number of these conditions, the group concluded that there would only be limited value in pursuing further research into smoked cannabis, because effective treatments were already available. However, they did recommend new controlled studies on smoked cannabis since current research did not provide definitive answers on its risk/benefit profile. The consensus was that in these research studies, smoked cannabis must meet the same standards as other medications in terms of effectiveness and safety.

Given that delta-9-tetrahydrocannabinol (dronabinol, the generic and Marinol®) is marketed to treat nausea and vomiting associated with chemotherapy and appetite stimulation in AIDS patients, the expert group suggested that the effects of smoked cannabis on these conditions be evaluated and studied to draw comparisons between smoked cannabis and synthetic THC.

Experts also specifically suggested that NIH use its resources to develop a smoke-free inhaled delivery system for cannabis or THC to eliminate the negative health effects of smoking in research trials.

### **Institute of Medicine Report**

In 1997, the White House Office of National Drug Control Policy (ONDCP) requested that the Institute of Medicine (IOM) conduct a review of the scientific evidence regarding the potential health benefits and risks of cannabis and its component cannabinoids. In 1999, the IOM issued the report *Cannabis and Medicine: Assessing the Science Base* that became the foundation of study into “medical marijuana” (Joy JE, Watson, Jr. SJ & Benson JA, 1999). IOM made a series of recommendations pertaining to the use of cannabis in medical treatment that revolve around the need for more research and evaluation.

In its report, IOM made the following recommendations (Joy JE, Watson, Jr. SJ & Benson JA, 1999):

- *Recommendation 1:* Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.
- *Recommendation 2:* Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

- *Recommendation 3:* Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.
- *Recommendation 4:* Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which cannabis use is prevalent.
- *Recommendation 5:* Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.
- *Recommendation 6:* Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:
  - failure of all approved medications to provide relief has been documented,
  - the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
  - such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and
  - Involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

The IOM clearly stated that the purpose of short-term *studies* with smoked cannabis would serve, at best, as preliminary support for the development of cannabis-based or cannabinoid modern medications. “The goal of clinical trials of smoked cannabis **would not be to develop cannabis as a licensed drug, but rather to serve as a first step toward the possible development of nonsmoked rapid-onset cannabinoid delivery systems** (emphasis added)” (Joy JE, Watson, Jr. SJ, & Benson JA, 1999). Specifically, IOM stressed that there is “little future in smoked marijuana.”

The IOM acknowledged that, until a nonsmoked rapid-onset cannabinoid drug delivery system became available, there was “no clear alternative” for people suffering from chronic conditions that might be relieved by smoked cannabis. The IOM suggested that one “possible approach” would be to treat patients as *n*-of-1 clinical trials, in which “patients are fully informed of their status as experimental subjects using a harmful drug delivery system. It recommended that their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions.” Under the current system of cannabis distribution by dispensaries, with limited oversight by physicians, these patient protections and data-collection functions are wholly absent.

## **Professional Organizations**

### **American Medical Association**

In both 1997(Council on Scientific Affairs Report 10, 1997) and 2001, the AMA issued reports on the scientific data relevant to the medical utility of cannabis (Council on Scientific Affairs Report 6, 2001). In November 2009, the AMA's Council on Science and Public Health (CSAPH) revised several of its policy statements on cannabis. The organization retained its previous recommendations for: 1) further adequate and well-controlled studies into cannabis and cannabinoids; 2) urging the NIH to facilitate grants applications for, and the conduct, of such trials; and 3) permitting free and unfettered exchange of information on treatment alternatives between physicians and patients, which should not subject either party to criminal sanctions.

In the Executive Summary, CSAPH noted that short-term clinical trials suggest that smoked cannabis has efficacy in certain medical conditions (a conclusion presumably further analyzed in the body of the report, which has not yet been published). In its Recommendation, AMA urged that cannabis's status as a schedule I drug be "reviewed." The purpose of such review would be to ascertain whether rescheduling could facilitate the conduct of clinical research and the "development of cannabinoid-based medicines and alternate delivery methods." AMA emphasized that this recommendation should **not** be viewed as an "endorsement of state-based medical cannabis programs, legalization of marijuana or that scientific evidence on the therapeutic use of cannabis meets the current standard for a prescription drug product" (Council on Science and Public Health Report 3, 2009). The report stressed "the patchwork of state-based systems that have been established for 'medical marijuana' is woefully inadequate in establishing even rudimentary safeguards that normally would be applied to the appropriate clinical use of psychoactive substances. The future of cannabinoid-based medicine lies in the rapidly evolving field of botanical drug substance<sup>10</sup> development, as well as the design of molecules that target various aspects of the endocannabinoid system."<sup>11</sup>

### **American College of Physicians**

In 2008, the American College of Physicians' (ACP) Health and Public Policy Committee (HPPC) composed a position paper on the medical uses of cannabis that followed the lead set forth by IOM. Their positions include (American College of Physicians, 2008):

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<sup>10</sup> For the meaning of "botanical drug substance," see discussion of the FDA Botanical Guidance, below.

<sup>11</sup> At its 2010 Interim Meeting, the AMA House of Delegates voted to amend current policy by urging the creation of a "special" schedule for cannabis (rather than moving cannabis to Schedule II), for the purpose of facilitating clinical research. <http://www.ama-assn.org/assets/meeting/2010i/i-10-annotated-k.pdf>.

- *Position 1:* ACP supports programs and funding for rigorous scientific evaluation of the potential therapeutic benefits of medical marijuana and the publication of such findings.
  - Position 1a: ACP supports increased research for conditions where the efficacy of marijuana has been established to determine optimal dosage and route of delivery.
  - Position 1b: Medical marijuana research should not only focus on determining drug efficacy and safety but also on determining efficacy in comparison with other available treatments.
- *Position 2:* ACP encourages the use of nonsmoked forms of THC that have proven therapeutic value.
- *Position 3:* ACP supports the current process for obtaining federal research-grade cannabis.
- *Position 4 (as amended):*<sup>12</sup> ACP urges an evidence-based review of marijuana’s status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana’s safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its smoked form.
- *Position 5:* ACP strongly supports exemption from federal criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for physicians who prescribe or dispense medical marijuana in accordance with state law. Similarly, ACP strongly urges protection from criminal or civil penalties for patients who use medical marijuana as permitted under state laws.

In an addendum to the position paper, ACP addressed concerns raised that it was promoting smoked marijuana as medicine. In this response, ACP states that it “has not advocated for the long-term use of smoked marijuana; rather, the paper explicitly discusses the harm associated with chronic use of smoked marijuana and stresses the need for development of nonsmoked forms of cannabinoid delivery systems strictly for therapeutic purposes supported by the evidence” (American College of Physicians, 2008). ACP also stressed that it “shares the concerns expressed by some about state ballot initiatives or legislation that can undermine the federal regulatory structure for assessing the safety and efficacy of new drugs before such drugs can be approved for therapeutic use.”

### **American Nurses Association**

In December 2008, the American Nurses Association (ANA) published the following statement on marijuana:

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<sup>12</sup> ACP’s original recommendation seemed to suggest that it was calling for the reclassification of cannabis into a “more appropriate” schedule. After receiving extensive commentary on this point, ACP clarified its position to state that the evidence merits a review of cannabis’s Schedule I classification, but any change to that classification should occur only if the review established that the evidence was sufficient to justify the change.

The American Nurses Association supports (American Nurses Association, 2008):

- The education of registered nurses and other healthcare practitioners regarding appropriate evidence-based therapeutic use of marijuana including those non-smoked forms of delta-9-tetrahydrocannabinol (THC) that have proven to be therapeutically efficacious.
- Protection from criminal or civil penalties for patients using medical marijuana as permitted under state laws.
- Exemption from criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for healthcare practitioners who prescribe, dispense or administer medical marijuana in accordance with state law.
- Reclassification of marijuana's status from a Schedule I controlled substance into a less restrictive category.
- Confirmation of the therapeutic efficacy of medical marijuana.

## The Federal Position

### The Controlled Substances Act (CSA)

All controlled substances are assigned to one of five schedules under the Controlled Substances Act (CSA), depending on their medical usefulness and their potential for abuse.<sup>13</sup> Cannabis/marijuana, ibogaine, mescaline, and peyote are botanical hallucinogens listed in Schedule I. Schedule I substances are those said to have:

- A high potential for abuse;
- No currently accepted medical use in treatment in the US<sup>14</sup>; and

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<sup>13</sup> The following factors, often referred to as the "eight factor analysis," determine the schedule to which a substance is assigned:

1. Its actual or relative potential for abuse
2. Scientific evidence of its pharmacological effects
3. The state of current scientific knowledge regarding the drug
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already under control

21 U.S.C. sec. 811.

<sup>14</sup> In a proceeding which seeks to move a drug from Schedule I to Schedule II, the DEA will examine the following factors in determining whether the drug has a "currently accepted medical use":

1. The drug's chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.

See *Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131 (D.C.Cir. 1994). <sup>14</sup> See 57 F.R. 10499,10506. According to the DEA, a failure to meet any of the factors precludes a drug from having a currently accepted medical use. 57 Fed.Reg. at 10507. Only a product going through the FDA process could meet all these criteria.

- A lack of accepted safety for use under medical supervision (21 USC sec. 812(c) (Schedule I (c))).

Substances in Schedule II have:

- A high potential for abuse;
- A currently accepted use in treatment in the US or a currently accepted medical use with severe restrictions; and
- Abuse of the substance may lead to severe psychological or physiological dependence (21 USC sec. 812(c) (Schedule II (a))).<sup>15</sup>

Opium, poppy straw, concentrate of poppy straw, and coca leaves are botanical materials listed in Schedule II. At the time the CSA was enacted in 1970, modern prescription medications derived from these botanical starting materials had already been approved for marketing by the FDA.

Substances in Schedule I may only be used in research studies by investigators who 1) have protocols that have been approved by the FDA and 2) have received research registrations from the Drug Enforcement Administration (DEA). Therefore, all possession, cultivation, distribution, etc., of cannabis, even if permitted under various state “medical marijuana” laws, continues to be illegal under federal law. A physician, however, has a First Amendment right under the federal Constitution to provide a patient with *bona fide* medical advice, which may include recommending the use of cannabis for medical purposes, so long as the physician does nothing affirmatively to aid or abet a patient in obtaining cannabis (*Conant v. Walters*, 2002).<sup>16</sup>

## Federal Departments and Agencies

On a number of occasions since 1996, the Drug Enforcement Administration has closed cannabis dispensaries (*US v. Oakland Cannabis Buyers Cooperative*, 2001) In October 2009, the federal Department of Justice (DOJ) issued guidelines to prosecutors (U.S. Department of Justice, 2009) that, despite the publicity these guidelines received suggesting that the Obama administration was permissive towards “medical marijuana,” are actually quite narrow. At the outset, the provisions stress that marijuana is a “dangerous drug.” They confirm the (already-existing) policy that federal prosecution priorities should be focused on significant<sup>17</sup> traffickers, not small-scale individual users. Hence, U.S. attorneys are advised not to prosecute **patients** “with cancer or other serious illnesses” who are using cannabis as part of a “recommended treatment regimen consistent

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<sup>15</sup> 21 USC sec. 812(c) (Schedule II (a)). Substances in Schedules III-V have decreasing levels of abuse potential and are subject to lesser degrees of control.

<sup>16</sup> For a more detailed description of this issue, see California Medical Association, CMA ON CALL, document #1315, The Compassionate Use Act of 1996: The Medical Marijuana Initiative (Jan. 2010) [http://www.cmanet.org/bookstore/freeoncall2.cfm/CMAOnCall1315.pdf?call\\_number=1315&CFID=745764&CFTOKEN=27566287](http://www.cmanet.org/bookstore/freeoncall2.cfm/CMAOnCall1315.pdf?call_number=1315&CFID=745764&CFTOKEN=27566287) (accessed Feb. 18, 2010).

<sup>17</sup> Note: this term is broader than “major.”

with state law” or **caregivers** in “clear and unambiguous” compliance with state law who provide cannabis to such patients (California Attorney General, 2008). “Commercial enterprises,” however, and those entities whose “nonprofit” medical marijuana distribution activities are merely a pretext for for-profit endeavors, **are** subject to prosecution.<sup>18</sup>

Subsequent to the issuance of these DOJ guidelines, the DEA issued a statement:

These guidelines do not legalize marijuana. It is not the practice or policy of DEA to target individuals with serious medical conditions who comply with state laws authorizing the use of marijuana for medical purposes. Consistent with the DOJ guidelines, we will continue to identify and investigate any criminal organization or individual who unlawfully grows, markets, or distributes marijuana or other dangerous drugs (Drug Enforcement Administration, 2009).

Similarly, the Director of ONDCP stressed:

The Department of Justice's guidelines strike a balance between efficient use of limited law enforcement resources, and a tough stance against those whose violations of state law jeopardize public health and safety...Enforcing the law against those who unlawfully market and sell marijuana for profit will continue to be an enforcement priority for the U.S. government (Office of National Drug Control Policy, 2009).

The Department of Transportation (DOT) also emphasized that the guidelines would not impact the DOT's drug testing program: “The Department of Transportation's Drug and Alcohol Testing Regulation – 49 CFR Part 40, at 40.151(e) – does not authorize ‘medical marijuana’ under a state law to be a valid medical explanation for a transportation employee's positive drug test result” (DOT, Medical Marijuana Guidelines, 2009)

In light of these statements, the current position of the federal government is uncertain. Nevertheless, largely because of exaggerated media reports, the Obama administration is viewed as lenient toward “medical marijuana.” This has been followed by proliferation of dispensaries which results in virtually unrestricted distribution of cannabis.

## **Modern Medications and the FDA Approval Process**

In earlier days in Western medicine, herbs and other botanical products were common treatment options and remain so in many developing countries. By the end of the 20<sup>th</sup> century, however, these crude botanical mixtures and preparations had been replaced

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<sup>18</sup> The guidelines also allow prosecution of those distribution activities that **may be consistent** with state law (in case a state decides to pass very liberal legislation), if necessary to “serve important federal interests.”



by “modern” medications which were characterized by standardized, purified products whose active ingredients (AIs) were often of synthetic origin.

<b>Folk Remedies</b>	<b>Modern Medicines</b>
Use plant products whose composition is uncertain and unregulated.	Use highly purified or defined medications, often comprising synthetic chemicals.
Treat poorly defined illnesses or symptom with unknown basis (e.g. cough from TB, influenza, or etc.).	Treat specific illnesses.
Are based on little understanding of the pathophysiology of the disorders being treated.	Elucidate the nature of the illnesses.
Are based on little understanding of the role of “medicine” in the therapy.	Use medicines that have a recognized effect on pathological processes; often understand the mechanism of action.
Are used in inconsistent and hard-to-quantify amounts.	Are administered in controlled doses; delivery system provides predictable dose over defined period of time.

Even those medications that once originated in botanical material, e.g., digitalis, were ultimately comprised of synthetic AIs. Dosage forms and delivery systems were carefully tested to deliver a discrete, reproducible dose. The ever-increasing sophistication and rigor of the FDA approval process contributed to this trend.

That approval process has been developed over the past century to protect patient safety and welfare. It promotes the quality, safety, and efficacy of medications, and is supported by all major medical/health care organizations. Extensive preclinical and clinical testing -- the results of which are published in peer-reviewed journals -- provides a robust body of risk-benefit and pharmacological data, on which physicians depend in order to make informed prescribing decisions. The registration and inspection procedures ensure that the manufacturing process is conducted in accordance with validated quality control tools and measures. Manufacturers’ promotional activities are limited to those claims supported by the medication’s label. Medications are prescribed and dispensed under the close supervision of licensed health care providers, primarily physicians and pharmacists.

In addition, the FDA has recently indicated that medications, both with and without abuse potential, must develop special plans to identify, evaluate, and mitigate the medication’s risks (Department of Health and Human Services, Food and Drug Administration, 2010). Such plans must include, where relevant, the risks of abuse and diversion (Department of Health and Human Services, Food and Drug Administration, 2009).

By contrast, herbal products and other dietary supplements are subject to a far lesser degree of supervision. Composition and quality are uncertain; clinical data on safety and efficacy are limited; and physicians generally do not feel qualified to opine about specific products' risks and benefits for particular medical conditions (Dietary Supplement Health and Education Act of 1994). Various scholars have suggested that the FDA should more stringently regulate many dietary supplements (Cohen PJ, 2005). Generally, dietary supplements are ingested orally and lack abuse potential .<sup>19</sup>

Despite the reduced level of regulatory scrutiny and quality assurance, public interest in botanically derived treatments continues to rise. Acknowledging such interest, and the fact that technology has improved significantly in recent decades, the FDA issued a 2004 guidance document that sets forth the principles to which pharmaceutical manufacturers must adhere when developing prescription medications derived from complex botanical material (Food and Drug Administration, 2004). The Guidance permits some leniency in the biochemical characterization of a prospective botanical agent during the early stages of research; however, at the point of advanced clinical research (Phase III), or New Drug Application (NDA), a medication must meet all standards for a new chemical entity (NCE).

The document identifies three stages of development for a botanically derived medication: 1) Botanical Raw Material (BRM), 2) Botanical Drug Substance (BDS) and 3) Botanical Drug Product (BDP). **BRM** is the fresh or processed (e.g., cleaned, frozen, dried, or sliced) part of a single species of plant or a fresh or processed alga or macroscopic fungus. **BDS** is prepared from botanical raw materials by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. It may be available in a variety of physical forms, such as powder, paste, concentrated liquid, juice, gum, syrup, or oil. **BDP** is a botanical product that is intended for use as a drug, i.e., a finished drug product that is prepared from a botanical drug substance. Botanical drug products are available in a variety of dosage forms, such as solutions (e.g., teas), powders, tablets, capsules, elixirs, and topicals.

In 2006, the FDA rejected the contention that smoked herbal cannabis “is a safe and effective medication.” FDA stated that:

A past evaluation by several Department of Health and Human Services (DHHS) agencies, including the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA) and National Institute for Drug Abuse (NIDA), concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use.... If a drug product is to be marketed, disciplined, systematic, scientifically conducted trials are the best means to

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<sup>19</sup> On December 30, 2003, the FDA announced its intention to ban the marketing of ephedra (FDA, 2004).

obtain data to ensure that drug is safe and effective when used as indicated. Efforts that seek to bypass the FDA drug approval process would not serve the interests of public health because they might expose patients to unsafe and ineffective drug products. FDA has not approved smoked marijuana for any condition or disease indication (Food and Drug Administration, 2006).

This statement does not imply that FDA will reject all cannabis-based medications. Indeed, one cannabis-derived medication, Sativex®, is entering into Phase III trials in accordance with the Guidance (GW Pharmaceuticals, 2006).

### **“Medical Marijuana” and the Modern Medication Model**

The status of “medical marijuana” contrasts sharply with the critically important aspects of the modern medication model. First, crude herbal cannabis is not a homogeneous material; the term “medical marijuana” therefore does not refer to a single, consistent substance or entity. The composition of herbal material, including its THC content, varies widely depending on the strain, cultivation, storage, and harvesting practices, etc. The opium poppy can similarly vary in composition. Opium can be rich in morphine, thebaine, or oripavine (Drug Enforcement Administration, 2008). The methods of herbal cannabis administration—smoked/vaporized, baked goods, teas, infused honeys, elixirs, candies, etc.—also do not ensure that a patient receives an identifiable, standardized, and hence reproducible, dose. Patients therefore cannot be certain that they will experience the same degree of benefit or extent of side effects from time to time. Patients, particularly those unfamiliar with cannabis, may be unwittingly dosed excessively, and incur frightening or severely unpleasant effects. For example, in a media report, one patient with advanced cancer ingested 1/8 teaspoon of cannabis-infused honey that she had purchased at a dispensary. “After a few hours, she was hallucinating, too dizzy and confused to dress herself for a doctor's appointment. Then came vomiting far worse than her stomach upset before she took the drug” (Mathews AW, 2010).

Second, quality control mechanisms are generally absent. As a result, cannabis products may be contaminated with microbes.<sup>20</sup> Certain pathogens, such as aflatoxins, are not destroyed by heat (as in smoking or vaporizing) and are increasingly being recognized as an “underestimated source of neurological toxicity or infections such as aspergillosis.” Individuals who are using anti-inflammatory steroids or have compromised immune systems are especially vulnerable to such infections (Hazekamp A, 2006). Heavy metals and pesticides may also be present. Cannabis samples recently tested from dispensaries in

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<sup>20</sup> A number of bacteria that are pathogenic to humans have been found on cannabis, including: *Salmonella muenchen*, *Klebsiella pneumoniae*, *Euterobacter cloacae*, *E. agglomerans*, *Streptococcus* (Group D), *Thermoactinomyces candidus*, *T. vulgaris*, *Micropolyspora faeni*, *Aspergillus fumigatus*, *A. niger*, *A. flavus*, *A. tamarri*, *A. sulphureus*, *A. repens*, *Penicillium chrysogenum*, *P. italicum*, *Rhizopus stolonifer*, *Alternaria alternata*, *Curvularia lunata*, and *Histoplasma capsulatum*. See generally, McPartland JM. “Contaminants and adulterants in herbal Cannabis,” in *Cannabis and Cannabinoids—Pharmacology, Toxicology and Therapeutic Potential* (Grotenhermen F & Russo E eds.) (Haworth Press New York) 2002.

Los Angeles contained pesticide levels 170 times greater than that permitted for herbal products ( *People v. Hemp Factory V*, 2009).<sup>21</sup> The manufacturers of these products have essentially no accountability, and the FDA does not inspect their manufacturing facilities. Patients injured by harmful products have no legal recourse.

Third, distribution of cannabis products does not take place within the monitored and regulated channels of supply for pharmaceuticals, but rather through dispensaries. These products are not labeled with content information, or with warnings and instructions for proper use, despite the fact that this is a requirement for all medical products under both state and federal law (California Sherman Food, Drug, and Cosmetic Act). Dispensary personnel who are not licensed medical practitioners offer medical advice concerning the efficacy or appropriateness of various products.

Finally, appropriate physician supervision is virtually unavailable. As indicated above, all state “medical marijuana” laws place physicians in an untenable position—on the one hand, being appointed the gatekeepers of a patient’s access to cannabis; on the other, having no access to the information necessary to provide meaningful advice and supervision. Reliable data—essential to a physician’s ability to assess a treatment option--are not being generated by the existing system of distribution and use. There is no mechanism for collecting data reflecting efficacy or adverse events; therefore, the medical community is precluded from knowing whether specific medical conditions are being improved, to what extent, and in which percentage or subgroup of patients, nor whether there are contraindications, drug-drug interactions, etc.

It is not surprising that in sessions at national medical conferences describing “New Therapeutic Developments,” herbal cannabis is almost never mentioned, despite its prominence in the media. Without a foundation of rigorous data, developed in clinical trials of proper length and design, and published in peer-reviewed journals, no cannabis product can ever gain entrance into the physician’s armamentarium and thereby become available to patients as a legitimate option among various treatment choices. Therefore, if it continues in its present form, the current cannabis distribution system has the unfortunate--even ironic--effect of **preventing** the vast majority of patients, who wish to be able to obtain meaningful guidance, advice, and supervision from their treating physicians, from obtaining access to cannabis-based medications.

Physicians should carefully consider their ethical and professional responsibilities before issuing a cannabis recommendation to a patient. A physician should not advise a patient to seek a treatment option about which the physician has inadequate information regarding composition, dose, side effects, or appropriate therapeutic targets and patient populations. State medical boards have indicated that physicians who discuss cannabis with a patient must adhere to the relevant standard of care and follow the basic

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<sup>21</sup> In 2005, a cannabis advocate died from a neurological condition believed to have resulted from handling cannabis contaminated by pesticides, which was being distributed through cannabis dispensaries. (Gardner F, 2005.)

professional tenets of good patient care: a physical examination, medical history, review of past medical treatments, development of a treatment plan, follow up and continuing oversight (Medical Board of California, 2004). Failure to do so may result in a finding of unprofessional conduct and significant sanctions, including license suspension or revocation (Medical Board of California, 2009). A physician's professional liability coverage may also not extend to harm resulting from a patient's use of cannabis upon the physicians' recommendation (Educating Voices, 2003).

This lack of effective physician oversight poses one of the greatest dangers to patients in the "system" by which cannabis is made available for ostensible medical use. The impact of this absence of professional monitoring is exacerbated by the fact that the potency of cannabis herbal material and cannabis products has risen significantly over the last few decades.<sup>22</sup> Such increased potency may heighten the risk of addiction (National Center on Addiction and Substance Abuse, 2008). This is particularly problematic in light of the fact that, increasingly, adolescents are obtaining "cards" which enable them to purchase and use cannabis with legal impunity. A number of adolescent psychiatrists have expressed concern at the rapidly increasing number of young patients who enter treatment for cannabis dependence but who have "cards" facilitating their continued use (Thurstone C, 2010). Furthermore, several studies have revealed that a very large percentage of individuals have sought cannabis cards in order to treat anxiety or depression, rather than nausea/vomiting from cancer chemotherapy, HIV, or pain and that almost all of those applicants initiated cannabis or other substance use during adolescence (Gardner F, 2006; O'Connell TJ & Bou-Matar CB, 2007). Such individuals require close physicians supervision to ensure that they are not developing or maintaining cannabis dependence, rather than attempting to alleviate a medical condition. Finally, individuals who smoke or vaporize high-potency cannabis are likely to experience intoxication, since inhalation rapidly raises plasma and brain levels of THC (Huestis MA, Henningfield JE, Cone EJ, 1002; Huestis MA, 2007). This may prevent both physicians and patients from identifying disease progression and hinder patients from obtaining appropriate treatment (Medical Board of California, 2004)<sup>23</sup>.

### **What Has Been Tried in Other Countries?**

Both Canada and the Netherlands have government-supervised programs for distributing cannabis for medical use. In Canada, court rulings mandated that the government establish a procedure through which patients could qualify to cultivate and possess cannabis for medical purposes. Subsequently, the government was required itself

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<sup>22</sup> The University of Mississippi has been analyzing the THC levels of seized cannabis for over 30 years. In that period, those levels (for domestic cannabis seizures) have increased from an average of 1.7% to 13%. See University of Mississippi Marijuana Potency Monitoring Project, [www.whitehousedrugpolicy.gov/publications/pdf/mpmp\\_report\\_104.pdf](http://www.whitehousedrugpolicy.gov/publications/pdf/mpmp_report_104.pdf).

<sup>23</sup> "The physician should determine that medical marijuana use is not masking an acute or treatable progressive condition, or that such use will lead to a worsening of the patient's condition."

to establish a regulated source of supply (Health Canada, Marijuana Medical Access Regulations, 2001).

Physicians have voiced serious concerns about this system. The Canadian Medical Association (CMA) stated:

Physicians are not in a position to counsel patients regarding the use of marijuana. Specifically, they are unable to provide thorough and necessary information regarding such issues as proper dosage, marijuana's interaction with other drugs or its impact on other pre-existing medical conditions... Lack of information on the indications, risks and benefits of medicinal marijuana hinders [a physician's] ability to inform properly patients and has the potential to threaten the patient-physician relationship. **CMA does not support physicians controlling access to substances for which routine pre-market regulatory review of safety, purity and efficacy, as required for current prescription drugs, has not occurred. (Canadian Medical Association, 2001)**

Physicians for a Smoke-Free Canada concurred:

First, since marijuana has not been thoroughly tested as a medicine, most physicians are familiar neither with its potential benefits (if any), nor with the dosage required to achieve those benefits. Second, when a patient is requesting smoked marijuana, the risks associated with smoking, coupled with the lack of clinical knowledge about specific benefits, make any accurate approximation of the risk to benefit ratio of treatment impossible (Physicians for a Smoke-Free Canada, 2002).

The Canadian Medical Protective Association voiced the same objections:

Given the fact that many physicians would not have the necessary knowledge about the effectiveness, risks or benefits of marijuana, we believe it is unreasonable to make physicians [the] gatekeepers in this process (Wharry S, 2002; Canadian Medical Protective Association, 2008).

In 2005, the Marijuana Medical Access Regulations (MMAR) regulations were revised to remove the requirement that physicians recommend a specific daily dose, form and route of administration. However, physicians are still required to indicate, in their medical declaration, the daily amount, form, and route of administration that the applicant intends to use. Although physicians no longer must state that the benefits of cannabis outweigh the risks, applicants must still declare that they have discussed the risks with the physician who signs the medical declaration. CMPA notes that the amended Regulations "represent an improvement," but "do not address all the CMA's and CMPA's previously expressed concerns."<sup>24</sup>

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<sup>24</sup> CMPA advises their members to obtain a release from liability from a patient for whom the physician has approved the use of cannabis.

Under the Health Canada program, cultivation is required to be conducted under Good Manufacturing Practices. Furthermore, in order to ensure that the microbial content remains at acceptable levels, the cannabis is irradiated before it is provided to patients (Health Canada, Product Information Sheet, 2008; Hazekamp A, 2006).<sup>25</sup> The dried cannabis has a THC level of  $12.5 \pm 2\%$ . Health Canada provides information to both physicians and to patients concerning the use of cannabis, including potential side effects (Health Canada, Product Information Sheet, 2008). Nevertheless, the system is foundering. An estimated 400,000-1,000,000 Canadians use cannabis for “self-identified” medical purposes, but approximately 4,029 persons have government authorizations to possess cannabis. Fewer than 20% of those access cannabis from Health Canada.<sup>26</sup> Detractors of the program claim, among other things, that the government authorization process is too lengthy and cumbersome; relatively few physicians will sign the necessary form; and the quality of the cannabis is not satisfactory (although it is on average 12% THC). They further claim that patients wish to select different strains for various medical conditions; and dosing limits confine patients to 5 grams a day, unless a physician is willing to explain a patient’s need for a higher daily intake (Belle-Isle L, Hathaway A, 2007; Canwest News Service, 2010). As a result, patients obtain their cannabis—and their information about the medical uses of cannabis and cannabis products-- from different “compassion clubs.”

In addition to criticisms from health care providers and patients, Canada has also incurred a reprimand from the International Narcotics Control Board (INCB), which believes that Canada is operating outside of its obligations under international treaties. In the aftermath of the INCB’s statement, governmental authorities have undertaken to review the Canadian program (Edwards S, 2010).

The situation in Canada demonstrates that even government-supervised cannabis cultivation and distribution programs are **not** sufficient to enable cannabis to become a legitimate medication that physicians are (or should be) comfortable prescribing. In order for cannabis-based medications to become broadly available to patients **through their treating physicians**, those medications must go through the conventional domestic medication approval processes.

## **Existing Research: What Do We Know and What Do We Still Need to Determine?**

### **Issues for Additional Research**

Considerable analytical and preclinical research and clinical investigations have been conducted with cannabinoid agonists, antagonists, and other compounds that affect

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<sup>25</sup> The Netherlands has a similar program. That cannabis, too, is irradiated to reduce microbial levels.

<sup>26</sup> As of June 2009, 4029 persons were authorized to possess cannabis, and 2841 persons were authorized to cultivate cannabis for medical purposes (2360 of which hold a personal use production license; 481 hold a designated-person production license). However, only 798 are currently obtaining cannabis from Health Canada; 891 have obtained seeds for cultivation; and 188 persons have received both. <http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/2009/june-juin-eng.php>

the cannabinoid receptor system. In examining such research, it is essential to avoid drawing excessively broad conclusions about the benefits and risks of smoked cannabis in humans from the results of published studies involving other preparations and other research settings.<sup>27</sup> For example, preclinical research studying synthetic THC, *in vitro* or *in vivo*, may offer intriguing possibilities for future clinical research, but it is certainly not determinative of the benefit/adverse event profile of smoked cannabis (or THC) in humans. Evidence that THC can inhibit malignant tumor growth in rodents does not mean, or even suggest, that smoking cannabis can prevent or cure cancer (Guzman M, 2003). Such studies provide at best a foundation for pursuing small pilot studies of a cannabinoid formulation in humans (Guzman M, et al, 2006). The effects of pure oral THC may differ significantly from that of smoked cannabis, because of both the formulation and the very different mode of delivery. Even different non-smoked cannabinoid formulations may exert notably disparate effects, depending on the cannabinoid composition and the method of administration. Finally, the effects of cannabis or cannabinoids in experimental pain models may not indicate how patients with chronic pain conditions would respond: “The respective mechanisms underlying the whole variety of chronic pain syndromes may considerably differ from acute nociception” (Hazekamp A & Grotenhermen F, 2010).

Current research reports and reviews rarely acknowledge that the composition and cannabinoid profile of modern herbal cannabis may be very different from that which existed centuries or even decades ago. Although discussions of cannabis commonly begin with the claim that “cannabis has been used therapeutically for hundreds, if not thousands, of years,” these research reports or reviews fail to point out that the cannabis plant has been significantly modified over that period through breeding techniques and modern cultivation practices. The widespread use of sinsemilla (the bud of the unfertilized female plant), coupled with sophisticated indoor cultivation projects, have in many cases increased THC levels considerably above those present in cannabis even 40 years ago.

In addition, selective breeding techniques have resulted in cannabis plants almost totally devoid of cannabidiol (CBD), a non-psychoactive cannabinoid with important therapeutic potential. In the past, a harvest of wild cannabis would have often been composed of approximately half THC and half CBD (of its major cannabinoids) (Potter DJ, Clark P, Brown MB, 2008). In animal models and some human studies, CBD has been shown to have analgesic, anti-psychotic, anticonvulsant, neuroprotective properties (Mechoulam R, Maximillian P, Murillo-Rodriquez E, et al, 1974; Russo E, Guy GW, 2006; Pertwee RG, 2004). There is also evidence that CBD may mitigate some of the negative effects of THC, such as psychoactivity (Karniol IG, Carlini EA, 1973; Karniol IG, Shirakawa I, Kasinski N, et al, 1974). Numerous reports have confirmed that CBD is almost entirely absent from modern black market cannabis (Potter DJ, Clark P, Brown MB, 2008). Because of these trends, modern herbal cannabis available in dispensaries may have very different effects than those reported centuries or even decades ago. The absence of CBD, coupled with higher levels of THC, may have adverse effects on patients, particularly in chronic use

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<sup>27</sup> Case studies, surveys, and non-controlled studies are beyond the scope of this report and will not be examined.



(DiForti M, et al, 2009; Sterling E, 2010). More research is needed to elucidate the effects of different cannabinoid (especially THC: CBD) ratios.

Dose-response relationships also require further research. Cannabinoids are known to exhibit biphasic effects, i.e., a lower dose may relieve a symptom but a higher dose may exacerbate it (Health Canada, Information for Health Care Professionals, 2003). A clinical study of smoked cannabis in experimental pain illustrates this well (Wallace M, et al, 2007). Furthermore, since patients vary widely in their response to cannabinoids, inadequate dosing or titration, e.g., the use of fixed doses may cause a clinical study to be negative, even if the investigative agent might otherwise have been expected to have therapeutic value (Strassler F, et al, 2006).

The method of medication delivery may also markedly affect both the extent of efficacy and range of side effects. The IOM has stated that oral dronabinol has low bioavailability and a prolonged onset of action, making it extremely difficult for patients to adjust their dose (Joy JE, Watson, Jr. SJ, & Benson JA, 1999). Psychoactivity, often in the form of dysphoria, is a problem and may prevent a patient from consuming a dose large enough to have therapeutic effect. It has been reported that some cannabis dispensaries prepare elixirs, honeys, baked goods, and candies, but there are no reliable data to indicate whether these preparations are more efficacious and/or better tolerated than oral dronabinol.

Different subgroups of patients may have different responses to cannabis and cannabinoids. Patients with debilitating and/or chronic medical conditions, elderly patients, and those who are cannabis-naïve may be more sensitive to CNS and other side effects. In addition, there is evidence of a gender difference in responsiveness to cannabinoids, particularly with regard to analgesia (Hazekamp A & Grotenhermen F, 2010).

### **Results of Controlled Clinical Trials**

Cannabinoid research—both preclinical and clinical—has increased almost exponentially in the past 20 years. A number of thorough reviews have been published which describe these studies (Joy JE, Watson, Jr. SJ & Benson JA, 1999; Ben Amar M., 2006; Russo EB, 2008; Hazekamp A & Grotenhermen F, 2010; Health Canada, Information for Health Care Professionals, 2003). Unfortunately, most literature reviews structure their analyses by the type of disease state, rather than the specific type of cannabis or cannabinoid intervention that was used to study that disease state. For the reasons stated above, this has the result of creating confusion and uncertainty, since different cannabis- and cannabinoid-preparations (with different formulations and dosage forms) may have different effects. Therefore, the brief summary of recent studies described below will focus on the type of cannabis or cannabinoid medication. In a limited number of studies, two such medications were compared against placebo. In such cases, the studies are generally mentioned twice.

## Oral Cannabinoid Preparations

### Dronabinol

Dronabinol (synthetic) is the best-known oral cannabinoid preparation.<sup>28</sup> The FDA approved it in 1985 for treatment of nausea and vomiting associated with cancer chemotherapy in patients who had failed adequately to respond to existing antiemetic treatments, and in 1992 for anorexia associated with weight loss in patients with AIDS. It showed efficacy in early studies by comparison to then-available anti-emetics (Council on Scientific Affairs Report 6, 2001). It has not, however, been compared with more recent anti-emetic medications, which have much better efficacy. One study has shown efficacy in delayed chemotherapy-induced nausea and vomiting comparable to ondansetron, although the combination of dronabinol and ondansetron did not provide benefit beyond that observed with either agent alone (Meiri E, et al, 2007). It did not show efficacy in a trial comparing an oral cannabis extract (Cannador®), THC and placebo on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome and was not more efficacious than megestrol acetate (Jatoi A, et al, 2002; Strasser F, et al, 2006). For a study investigating dronabinol and smoked cannabis on viral load and food intake in HIV positive patients, see discussion below.

Studies of Marinol® as an analgesic and/or antispasmodic have been mixed. Early studies found it efficacious in reducing cancer pain at doses of 10, 15, and 20 mg. but side effects were prominent (Noyes Jr R, Brunk SF, Avery DH, Canter A, 1975). It has been found effective in central neuropathic pain in multiple sclerosis, but not in postoperative pain (Buggy DJ, Toogood L, Maric S, et al, 2003; Svendsen KB, Jensen TS, & Bach FW, 2004). The Institute of Medicine has stated that, "It is well recognized that Marinol's oral route of administration hampers its effectiveness because of slow absorption and patients' desire for more control over dosing" (Joy JE, Watson Jr. SJ, & Benson JA, 1999).

In a large trial of patients with multiple sclerosis, dronabinol<sup>29</sup> did not show objective improvement in spasticity measured on the Ashworth scale, the primary endpoint. There was objective improvement in mobility and subjective improvements in spasticity, spasm, pain and sleep quality (Zajicek J, et al, 2003). In a one-year follow up, patients showed a small objective improvement in spasticity, as well as highly significant subjective improvements in spasticity, spasm, pain, tiredness and sleep (Zajicek J, et al, 2005).

### Cesamet®

Cesamet® (Nabilone) is a synthetic cannabinoid analogue that is believed to be more potent than THC. It is approved for the treatment of nausea and vomiting associated

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<sup>28</sup> The branded name is Marinol®. In Schedule III of the CSA, the substance is defined as: dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a US Food and Drug Administration approved product. 21 CFR sec. 1308.13(g)(1). Generic versions of Marinol® are now on the market.

<sup>29</sup> This study compared dronabinol, Cannador® and placebo.

with cancer chemotherapy in patients who have failed adequately to respond to available antiemetics. In one small study, it has been shown to reduce spasticity-related pain in patients with upper motor neuron syndrome (Wissel J, et al, 2006). In a controlled study of patients undergoing various surgical procedures, high dose Nabilone in the presence of morphine PCA was associated with an increase in pain scores (Beaulieu P, 2006).

### **Cannador®**

Cannador® is an oral cannabis extract (encapsulated), with reportedly a 2:1 ratio of THC to CBD. It is under investigation in Europe by the Institute for Clinical Research. In a study comparing Cannador® with dronabinol and placebo on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome, no differences were found between Cannador®, THC or placebo (Strasser F, et al, 2006). In a large study of patients with multiple sclerosis, it did not show objective improvement in spasticity measured on the Ashworth scale, although there was subjective improvements in spasticity, spasm, pain and sleep quality (Zajicek J, et al, 2003). In a one-year follow up, patients showed a small objective improvement in spasticity, as well as highly significant subjective improvements in spasticity, spasm, pain, tiredness and sleep (Zajicek J, et al, 2005).

In analgesic studies, Cannador® has shown a modest dose-dependent decrease in rescue analgesia requirements in postoperative pain (Holdcroft A, Maze M, 2006).

### **Smoked/vaporized Herbal Cannabis**

In 2003, a controlled residential study found that both smoked cannabis and dronabinol had beneficial effects on appetite and weight gain in HIV positive patients on stable anti-retroviral therapy. In the course of the 21-day treatment period, there was no adverse effect on viral load or the number of CD4+ and CD8+ lymphocytes, nor did the two forms of cannabinoids interfere with the protease inhibitors taken by the patients (Abrams DJ, et al, 2003). A subsequent study demonstrated that both smoked cannabis and dronabinol increased food intake in experienced cannabis smokers, although this increase paralleled increased ratings of intoxication (Hanley M, Rabkin J, Gunderson E, Foltin RW, 2005).

In 1999, the Center for Medicinal Cannabis Research (CMCR) was established pursuant to legislation commissioning the University of California to establish a research program to investigate the therapeutic potential of cannabis and cannabinoids. Over the course of the next ten years, CMCR approved and funded fifteen clinical studies, including seven controlled clinical trials, of which five have completed and two are ongoing (Center for Medical Cannabis Research, 2010). Five clinical studies have been published in peer-reviewed journals. Three of these studies involved neuropathic pain; a fourth involved experimental pain, and one involved a pilot study for a cannabis delivery device (Abrams DI, et al, 2007; Wilsey B, et al, 2008; Ellis RJ, et al, 2009).

These studies have provided preliminary evidence of analgesic efficacy which suggest that further trials of cannabis-derived and cannabinoid medications in neuropathic

pain of various origins should be pursued to identify desirable cannabis-based or cannabinoid formulations and modes of delivery. The results of these studies cannot, however, be said to “prove” that smoked cannabis should be made available to patients with chronic pain conditions. Each study was conducted in a small number of patients and was of very short duration. In almost all cases, the patients were cannabis-experienced. Indeed, in one study, the authors noted that only cannabis experienced patients were entered into the study in order “to reduce the risk of adverse psychoactive effects in naïve individuals” (Wilsey B, et al, 2008). Therefore, the risk/benefit profile in these patients—particularly the incidence of adverse CNS events--cannot be generalized to cannabis-naïve patients. In fact, in one study, an incident of acute cannabis-induced psychosis occurred in a cannabis-naïve patient, resulting in his withdrawal from the study (Ellis RJ, et al, 2009).

Even among cannabis-experienced patients, the level of adverse events was notable; in one study, cognitive impairment was especially prominent (Wilsey B, et al, 2008). This could suggest that an inhalation mode of delivery may not be optimal. Such rapid delivery of THC may not be necessary in patients with chronic conditions, so long as the dosage form enables patients to titrate their dosing level to individual benefit/tolerability over several days. The cannabis available in these studies was a maximum of 8% THC. In one study, cannabis of only 3.5% generated a significant CNS side effect profile (Abrams DI, et al, 2007). Such CNS side effects would no doubt be even more prevalent if patients were to use higher-potency cannabis, such as that available in dispensaries. Finally, the effectiveness of the blinding is subject to question, since the patients were cannabis-experienced and could be expected to be able to distinguish active from placebo. In the Ellis study, blinding was evaluated; 93% of those patients assigned to receive cannabis accurately guessed that they were on active medication, whereas the patients assigned to placebo generally did not guess correctly (Ellis RJ, et al, 2009).

The results of these studies, while quite interesting, constitute at most the early stages of cannabinoid medication development. Neither the efficacy nor the adverse events in these short-term acute studies can be extrapolated to chronic use. Alone, they could not form the basis of FDA approval, nor of cannabis rescheduling.

### **Oromucosal/sublingual Cannabis-derived Preparations**

Sativex® (nabiximols) is a botanically derived cannabis extract with a defined 1:1 ratio of THC to CBD and delivered as an oromucosal spray.<sup>30</sup> Sativex® has shown positive results as an adjunctive treatment in controlled studies involving patients (with previously intractable symptoms who remained on all their existing medications) with brachial plexus avulsion (Berman JS, Symonds C, Birch R, 2004), central neuropathic pain in multiple sclerosis (Rog DJ, Nurmillo T, Friede T, et al, 2005), spasticity in multiple sclerosis (Collins C, Davies P, Mutiboko IK, Ratcliffe S, 2007), rheumatoid arthritis (Blake DR, et al, 2006), peripheral neuropathic pain (Nurmikko TJ, Serpell MC, Hoggart B, et al, 2007), and pain associated with advanced cancer (Johnson JR, Burnell-Nugent M, Lossignol D, et al, 2010).

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<sup>30</sup> Sativex® is produced by GW Pharmaceuticals in the UK. Nabixomols is the US Adopted Name (USAN).

Interestingly, in the cancer pain study, nabiximols showed statistically significant analgesic effect compared with placebo, whereas a THC-predominant extract did not. This may suggest that the THC: CBD formulation has a different therapeutic impact compared to THC without CBD.

Symptom relief with nabiximols was maintained in long-term studies, without the need for dose escalation (Wade DT, Makela PM, House H, et al, 2006). Patients who abruptly withdrew from nabiximols did not exhibit a cannabis withdrawal syndrome (Budney AJ & Hughes JR, 2006) or any withdrawal symptoms requiring treatment. Intoxication scores remained low, even during dose titration (Wade DT, Makela PM, House H, et al, 2006). Sativex® does not induce psychopathology or impair cognition in cannabis-naïve patients with multiple sclerosis (Aragona M, et al, 2009). By contrast, smoked cannabis produces cognitive impairment in patients with Multiple Sclerosis (Ghaffaro O and Feinstein A, 2008).

Sativex® is approved in the UK, Spain, New Zealand, and Canada as an adjunctive treatment for spasticity in multiple sclerosis and may be available soon thereafter in other European Union countries under harmonized recognition procedures. Canada has also approved it under the Notice of Compliance with Conditions (NOC/c) as an adjunctive treatment for neuropathic pain in multiple sclerosis and for pain associated with advanced cancer pain. In the United States, it is undergoing advanced clinical studies in patients with advanced cancer whose pain has not been adequately relieved by strong (Step III) opioids.

## **Are There Principled Reasons for Exempting Cannabis from the Quality, Safety, and Efficacy Requirements of the Modern Medication Model?**

### **Is Cannabis Benign?--Risks and Side Effects**

Cannabis is not a “harmless herb.” According to the IOM, it is a “powerful drug with a variety of effects” (Joy JE, Watson, Jr. SJ & Benson JA, 1999). To be sure, all medications have potential side effects, some of them quite serious. During the course of controlled clinical trials (both pre- and post-marketing), many of these side effects are identified, and a medication’s benefit/risk profile can thereby be assessed, by both regulatory authorities and the medical profession. Ongoing physician supervision allows these risks to be managed, e.g., by dose adjustment, discontinuation of treatment, or rotation to/augmentation by an alternate or additional medication. Medication labels and inserts apprise patients of probable side effects. For example, patients should be warned of the risks of driving or operating heavy machinery while under the influence of cannabinoids (U.S. National Highway Traffic Safety Administration, 2004; Beirness DJ & Porath-Waller AM, 2009).<sup>31</sup> Cannabis products distributed by dispensaries lack this information.

A number of side effects may be of particular concern when cannabis is used in significant amounts daily, over a long period, in smoked form, by patients with debilitating

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<sup>31</sup> Inhalation of cannabis produces deficits in tracking, reaction time, visual function, and divided attention.

medical conditions. The acute effects of pure THC and high-THC cannabis that are relevant to medical use include intoxication (including dysphoria), anxiety (including panic attacks), hallucinations and other psychotic-like symptoms, somnolence, confusion, psychomotor impairment, cognitive impairment, dizziness, orthostatic hypotension, dry mouth <sup>32</sup>, and tachycardia (Joy JE, Watson, Jr. SJ & Benson JA, 1999). In clinical trials of cannabinoid medications, patients with pre-existing serious mental disorders, significant hepatic or renal impairment, epilepsy, cardiac conditions, or prior substance abuse/dependence are typically excluded. Nevertheless, patients with these conditions are routinely added to the "membership lists" of dispensaries.

The IOM recognized that these acute side effects are "within the risks tolerated for many medications" (Joy JE, Watson, Jr. SJ & Benson JA, 1999). As noted above, however, the side effects of other medications have been identified by means of extensive testing and examination in both nonclinical/preclinical and Phase I-III clinical trials, including large double-blind, placebo-controlled studies. The acute side effects of smoked cannabis have not been fully elucidated through such comprehensive testing. As a result of these potential side effects, which may more severely impact the elderly or those with hepatic or immune impairment, it is imperative that specific cannabis and cannabinoid medications are studied in particular medical conditions and patient populations, and patients using such medications in clinical practice should be properly supervised by their treating physicians. Under the current system in the 15 states that have "medical marijuana" laws, none of this data collection and physician supervision is taking place according to regulatory standards.

The chronic effects of inhaled cannabis are of special concern in the context of medical use. These chronic effects can be placed into several categories: the effects of chronic smoking and the effects of inhaled THC. Patients often use 1-5 grams a day of cannabis; this represents 1-8 cannabis cigarettes (Comeau P, 2007). The remaining patients in the federal Compassionate Use Program are provided with 300 cannabis cigarettes per month.<sup>33</sup>

Cannabis smoke contains many of the components of tobacco smoke. Smoking a cannabis cigarette can deposit as much as four times the amount of tar in the lungs, compared to smoking a tobacco cigarette (Wu TC, Tashkin DP, Djahed B, Rose JE, 1988). This effect results from the fact that cannabis cigarettes lack filters and cannabis smokers inhale more deeply and hold their breath longer than tobacco smokers hold theirs (Joy JE,

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<sup>32</sup> Dry mouth can cause gum disease, tooth decay, and mouth infections, such as thrush.

<sup>33</sup> The National Institute on Drug Abuse (NIDA) supplies cannabis to several patients under a single patient so-called 'compassionate use' Investigational New Drug Applications (IND). In 1978, as part of a lawsuit settlement by the Department of Health and Human Services (DHHS), NIDA began supplying cannabis to patients whose physician applied for and received such an IND from the FDA. In 1992, the Secretary [of Health and Human Services] terminated this practice, but decided that NIDA should continue to supply those patients who were receiving cannabis at the time.

<http://www.drugabuse.gov/about/organization/nacda/MarijuanaStatement.html>

Watson, Jr. SJ & Benson JA, 1999). There is no doubt that chronic cannabis smoking is harmful to the lungs (Tashkin DP, 2005; Diplock J and Plecas D, 2009).<sup>34</sup>

The inhalation of cannabis also poses a risk of abuse and dependency. As the IOM stated: “Adolescents, particularly those with conduct disorders, and people with psychiatric disorders, or problems with substance abuse appear to be at great risk for marijuana dependence than the general population.” Heavy cannabis use in adolescence is associated with a variety of neurocognitive deficits (Schweinsburg AD, Brown SA & Tapert SF, 2008). The high-potency cannabis now distributed by dispensaries could exacerbate these risks. The fact that adolescents have ready access to cannabis “cards,” without meaningful physician supervision, is particularly problematic.

These concerns are not vitiated by “vaporization,” currently popular with cannabis advocates. First, there are wide varieties of vaporizers available for purchase on the internet and at cannabis dispensaries, although the FDA has approved none of them as a medical device. They vary significantly in the extent to which they reduce toxic combustion products. Even the most sophisticated vaporizer, the Volcano®<sup>35</sup>, has not been demonstrated to eliminate all polyaromatic hydrocarbons, at least at higher temperatures (Gieringer D, St. Laurent J & Goodrich S, 2004). Even at lower temperatures, ammonia and acetaldehyde have also not been shown to be eliminated (Russo E, 2006; Bloor RN, Wang TS, Spanel P, & Smith D, 2008).<sup>36</sup> By contrast, carbon monoxide does not appear to be released by vaporization with the Volcano ® (Abrams DI, et al, 2007).

Second, the products of vaporization are dependent on the quality and composition of the underlying herbal material. If that material is not highly standardized, the composition of the vapor will be uncertain. Because these devices have not been fully tested through the FDA process it is uncertain whether herbal material contaminated with pesticides or microbes would transmit these contaminants into the vapor. Unless the vaporizer device has a lockout mechanism, variability in intra- and inter-patient inhalation patterns may make it unlikely that a known and reproducible dose will be delivered.

Third, vaporization does not improve the side effect profile exhibited by smoked cannabis, including its psychoactive effects. Like smoking, vaporization causes THC plasma levels to rise abruptly (Miller J, Meuwesen I, ZumBrunnen T, & de Vries M, 2005). Rapid delivery of THC to the plasma and brain increases the likelihood of intoxication and abuse liability, and may promote dependency (Samaha AN & Robinson TE, 2005). Again, such

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<sup>34</sup> In 2009, California’s Office of Environmental Health Hazard Assessment added cannabis smoke to its official list of known carcinogens. See, Tomar RS, Beaumont J, Hsieh JCY. Evidence on the Carcinogenicity of Marijuana Smoke. [http://www.oehha.ca.gov/prop65/public\\_meetings/pdf/cicslides060509.pdf](http://www.oehha.ca.gov/prop65/public_meetings/pdf/cicslides060509.pdf)

<sup>35</sup> The Volcano® is produced by Storz & Bickel GmbH & Co. KG in Germany. <http://www.storz-bickel.com/vaporizer/storz-bickel-company-vaporizer-manufacturer.html>.

<sup>36</sup> It is important that the FDA assess medical devices that deliver vaporization products to the lungs. The FDA has recently warned consumers about the dangers of toxic and carcinogenic chemicals contained in electronic cigarettes, touted as a smoke-free and less harmful alternative to smoking. FDA, FDA News Release, “FDA and Public Health Experts Warn About Electronic Cigarettes.” <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm>

rapid delivery is probably not necessary for patients with chronic conditions so long as the dosage form enables such patients to titrate their dose adequately and predictably (Russo E, 2006).<sup>37</sup> For example, rapid onset opioid medications, such as buccal fentanyl, are prescribed for patients with breakthrough pain, not with chronic persistent pain. In fact, patients with such persistent pain are often placed on extended release opioid medications once their individual daily dose is established through short-term release medications.

Finally, when cannabis joints or vaporizers are shared, dangerous pathogens can be spread amongst seriously ill patients (Zanocco V, 2005).

### **Could a Cannabis Preparation Achieve FDA Approval?**

As indicated above, the FDA has set forth the requirements for the development of a botanically based prescription medication. Those agency recommendations require that highly standardized cannabis herbal material (Botanical Raw Material) be developed into a Botanical Drug Substance and ultimately into a Botanical Drug Product. Under the Guidance document, it may be challenging for herbal material—even if standardized—to be approved, since the herbal material must also be incorporated into a defined and reproducible dosage form. As the AMA report recognized, “The future of cannabinoid-based medicine lies in the rapidly evolving field of **botanical drug substance development**, as well as the design of molecules that target various aspects of the endocannabinoid system” (American Medical Association, 2009). Smoked cannabis—particularly for chronic use—would no doubt pose risks that would be unacceptable to the agency. Improvements in vaporization technology would need to occur in order fully to eliminate all toxic combustion products and ensure a standardized and predictable dose.

None of this is impossible. Therefore, the obvious question arises: why, as a policy matter, should herbal cannabis be exempted from the modern medication model? Many new promising medications are under investigation, and suffering patients understandably seek to obtain access to them as early as possible. The FDA has established fast-track procedures<sup>38</sup> to facilitate this access, and compassionate access through Treatment INDs is often available during late-stage medication development.<sup>39</sup> Both the FDA and the federal courts, however, have concluded that seriously ill—even terminally ill—patients will not benefit on balance from products that have not completed the vast majority of steps leading to an approved medication (Abigail Alliance, 2008). In short, the concept of “medical necessity” is not sufficient to override the provisions of the Food, Drug and

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<sup>37</sup> Inhaled cannabis has a shorter duration of action than oral or other dosage forms.

<sup>38</sup> 21 C.F.R. secs. 312.80, 312.10, 314.500.

<sup>39</sup>The FDA may approve use of an investigational drug by patients not part of the clinical trials for the treatment of “serious or immediately life-threatening disease[s]” if there exists “no comparable or satisfactory alternative drug or other therapy,” if the drug is under investigation in a controlled clinical trial, and if the drug’s sponsor is actively pursuing marketing approval of the investigational drug with due diligence. 21 C.F.R. sec. 312.34.



Cosmetic Act (Abigail Alliance, 2008) or the Controlled Substances Act (United States v. Oakland Cannabis Buyers' Cooperative, 2001).

Allowing cannabis to circumvent the requirements of the FDA process sets a dangerous precedent for the future. For example, herbal products called "Spice," "Skunk," and "Sence" are currently becoming popular in the U.S. and Europe. These products contain herbal preparations that are "enriched" with synthetic cannabinoids, such as HU 210, which is much more potent than THC. These synthetic cannabinoids have been developed over the past 30 years for research purposes to investigate the endocannabinoid receptor system in non-human studies. Although these compounds have THC-like properties, they are much more potent than THC. Products containing these synthetic cannabinoids are marketed as "legal" alternatives to cannabis and are being sold over the internet and in tobacco and smoke shops, drug paraphernalia shops, and convenience stores. Could "Spice" advocates in the future contend that these products, too, should be made available to patients and other consumers without being tested through the FDA process? This is, indeed, a dangerously slippery slope.<sup>40</sup>

### **The Significance of Scheduling**

Both the AMA and ACP have recently questioned the status of cannabis's placement in Schedule I of the Controlled Substances Act.<sup>41</sup> Schedule II substances are, for the most part, subject to the same restrictions and requirements under the Controlled Substances Act, including manufacturing and procurement quotas, security measures, recordkeeping, import/export permits, etc. It may be useful, therefore, to examine what the rescheduling of cannabis (presumably to Schedule II) would and would not achieve. Cannabis advocates commonly urge that cannabis be rescheduled "so that it can be made available to patients on prescription." Rescheduling herbal cannabis alone would not, however, be sufficient to create a medication that physicians could prescribe and pharmacists could dispense. In order to be prescribable, any particular medication must have successfully completed the FDA approval process. The FDA does not approve "bulk" substances, such as cannabis (or raw opium or coca leaves), for marketing and direct prescription. Therefore, a specific cannabis-derived medication would have to be developed in accordance with FDA standards, which would require that it be standardized, formulated, tested, and administered in an appropriate delivery system." In order for a Schedule II substance to be made available by prescription, it

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<sup>40</sup> The DEA has recently acted on an emergency basis to place five such compounds in Schedule I. DOJ, DEA, "Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids into Schedule I," 75 Fed. Reg. 71636 (Nov. 24, 2010). This action will make possessing and selling these chemicals or the products that contain them illegal in the U.S. for at least one year while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals and products should be permanently controlled.

<sup>41</sup> Note cannabis is assigned to Schedule I under most state controlled substances laws, including California's.

must be contained in one or more specific dosage forms, as is the case for opium. Each and every one of such dosage forms must pass FDA muster” (Russo E, 2006).<sup>42</sup>

FDA approval of a specific cannabis Botanical Drug Product would constitute “currently accepted medical use in the US,” thereby allowing that medication to be rescheduled into Schedule II or below (*Grinspoon v. DEA*, 1984).<sup>43</sup> Such FDA approval, however, would not necessarily require the rescheduling of bulk cannabis, despite the fact that opium and coca leaves are in Schedule II. Although the Controlled Substances Act schedules apply to classes of substances, rather than specific medications, precedent has developed for “differential scheduling.” For example, synthetic dronabinol, in a specific FDA-approved formulation, is listed in Schedule III, while pure THC in any other form remains in Schedule I.<sup>44</sup> Similarly, Xyrem®, an approved treatment for narcolepsy, is classified in Schedule III, while “street” versions of GHB remain in Schedule I (Neuman A, 2004). Therefore, if such a specific cannabis medication were approved by the FDA and rescheduled by the DEA, bulk herbal cannabis could still remain in Schedule I.

Rescheduling of cannabis would also not allow pharmacists to compound cannabis products for large numbers of patients. The FDA has issued numerous warning letters to compounding pharmacists, emphasizing that:

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy, however, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). ***Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product or diluted dosages for children.***

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources

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<sup>42</sup> Interestingly, one prominent cannabis advocate, who has filed cannabis rescheduling actions, **does not contend** that rescheduling would make cannabis prescribable to patients. Gettman J. “Frequently Asked Questions about Medical Cannabis and Rescheduling.” [http://www.drugscience.org/lib/freq\\_qst.html](http://www.drugscience.org/lib/freq_qst.html).

<sup>43</sup> As noted above, fn 14, delineating the criteria that must be met in order for a substance to have a “currently accepted medical use in the US.” These criteria can only be satisfied by a robust body of scientific data, not by the enactment of state laws that decriminalize the use of cannabis for medical purposes. US Department of Justice, DEA, letter to Carl Olsen (Dec. 19, 2008) (denying a petition for rescheduling). [http://www.iowamedicalmarijuana.org/petitions/pdfs/dea\\_20081219.pdf](http://www.iowamedicalmarijuana.org/petitions/pdfs/dea_20081219.pdf)

<sup>44</sup> The DEA has recently issued a Notice of Proposed Rulemaking (NPRM) proposing to transfer certain generic dronabinol products to Schedule III. DOJ, DEA, “Listing of Approved Drug Products Containing Dronabinol in Schedule III,” 75 Fed. Reg. 67054 (Nov. 1, 2010).

against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA (FDA, Compliance Policy Guide, 2002; FDA, Warning Letter, 2006).

Rescheduling cannabis would not automatically reduce or otherwise affect federal criminal penalties for possession or trafficking. These statutes provide specific penalties for marijuana or for possessing a controlled substance without a lawful prescription.<sup>45</sup> Such statutes would require separate amendment in order for existing penalties to be modified, and this amendment process would involve different policy factors and considerations.

Cannabis rescheduling would also not necessarily allow the establishment of additional cannabis cultivation facilities to produce cannabis for research purposes. The United States is a signatory to the Single Convention on Narcotic Drugs 1961. That treaty requires that cannabis cultivated within the U.S. borders must be delivered to a national agency. In the US, the national agency is the National Institute on Drug Abuse (NIDA). NIDA has the exclusive authority over importing, exporting, wholesale trading, and maintaining stocks (Single Convention on Narcotic Drugs, 1961).<sup>46</sup> Only the University of Mississippi, under contract with NIDA, currently cultivates cannabis for research purposes (NIDA, 1997). The mandates of the treaty are not affected by cannabis's scheduling under US domestic law.<sup>47</sup>

There is one respect, however, in which the rescheduling of cannabis could facilitate research. If a physician-investigator possesses a registration (the CSA term for a license) to dispense an FDA-approved Schedule II controlled substance, he or she may conduct research on any Schedule II substance, as a "coincident activity" to his/her registration to dispense, without the need to obtain a separate research registration from the DEA. (Of course, any such research would still need to be approved by the FDA and an appropriate institutional review board, as well as perhaps by a state regulatory body.<sup>48</sup> By contrast, a separate registration is required for Schedule I research.<sup>49</sup> In addition, each registration is protocol-specific. If a researcher wishes to conduct a different study on the same Schedule I substance, he/she must obtain a separate registration. Furthermore, a Schedule II practitioner registration must be renewed every three years; whereas a Schedule I research registration must be renewed annually. Thus, any delays associated with obtaining and renewing a Schedule I research registration could be obviated by the rescheduling of cannabis to Schedule II. This situation, however, could also be resolved by a more limited statutory and regulatory change that permitted practitioners with Schedule II

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<sup>45</sup>See, e.g., 21 U.S.C. secs. 841,844.

<sup>46</sup> There is an exception for stocks held by manufacturers of pharmaceutical preparations. Art. 23, para. 2(e).

<sup>47</sup> For fuller discussion of the requirements of the Single Convention, see Department of Justice, DEA, Lyle E. Craker; Denial of Application, 74 *Fed. Reg.* 2101 (Jan. 14, 2009).

<sup>48</sup> 21 U.S.C. sec. 823(f); 21C.F.R. secs.1301.13.

<sup>49</sup> 21 C.F.R. sec.1301.18.

registrations to conduct Schedule I cannabis/cannabinoid research as a coincident activity to their existing registrations.

## Conclusions

“Cognitive dissonance” is a term that aptly describes the current approach to “medical marijuana.” Scientists recognize the public health harms of tobacco smoking and urge our young people to refrain from the practice, yet most cannabis consumers use smoking as their preferred delivery mechanism. The practice of medicine is increasingly evidence-based, yet some physicians are willing to consider “recommending” cannabis to their patients, despite the fact that they lack even the most rudimentary information about the material currently being consumed by patients (composition, quality, and dose, and no controlled studies provide information on its benefit and safety of its use in chronic medical conditions). Pharmaceutical companies are responsible for the harms caused by contaminated or otherwise dangerous products and tobacco companies can be held accountable for harms caused by cigarettes, yet, dispensaries distribute cannabis products about which very little are known, including their source. Efforts are being made to stem the epidemic of prescription drug abuse, including FDA-mandated risk management plans required for prescription medications, yet cannabis distribution sites proliferate in many states, virtually without regulation.

In order to think clearly about “medical marijuana,” one must distinguish first between 1) the therapeutic potentials of specific chemicals found in marijuana that are delivered in controlled doses by nontoxic delivery systems, and 2) smoked marijuana.

Second, one must consider the drug approval process in the context of public health, not just for medical marijuana but also for all medicines and especially for controlled substances. Controlled substances are drugs that have recognized abuse potential. Marijuana is high on that list because it is widely abused and a major cause of drug dependence in the United States and around the world. When physicians recommend use of scheduled substances, they must exercise great care. The current pattern of “medical marijuana” use in the United States is far from that standard.

If any components of marijuana are ever shown to be beneficial to treat any illness then physicians should prescribe those components by nontoxic routes of administration in controlled doses just all other medicines are in the U.S.

In order for physicians to fulfill their professional obligations to patients, and in order for patients to be offered the high standard of medical care that we have come to expect in the United States, cannabis-based medications must meet the same exacting standards that we apply to other prescription medicines. Members of the American Society of Addiction Medicine are physicians with expertise in addiction medicine with knowledge specific to the risks associated with the use of substances with high abuse potential. ASAM must stand strongly behind the standard that any clinical use of a controlled substance

must meet high standards to protect the patient and the public; the approval of “medical marijuana” does not meet this standard.

## **Recommendations**

ASAM asserts that cannabis, cannabis-based medications, and cannabis delivery devices should be subject to the same standards that are applicable to other prescription medications and medical devices and that these medications or devices should not be distributed or otherwise provided to patients unless and until such medications or devices have received marketing approval from the Food and Drug Administration.

ASAM recommends its members and other physician organizations and their members reject responsibility for providing access to cannabis and cannabis-based medications until such time that these materials receive marketing approval from the Food and Drug Administration.

ASAM rejects smoking as a means of drug delivery since it is inherently unsafe.

ASAM supports the need for federal regulatory standards for drug approval and distribution. ASAM recognizes that states can enact limitations that are more restrictive but rejects the concept that states could enact more permissive regulatory standards. ASAM discourages state interference in the federal medication approval process.

ASAM rejects a process whereby State and local ballot initiatives approve medicines because these initiatives are being decided by individuals not qualified to make such decisions (based upon a careful science-based review of safety and efficacy, standardization and formulation for dosing, or provide a means for a regulated, closed system of distribution for marijuana which is a CNS drug with abuse potential).

ASAM asserts that physician organizations operating in states where physicians are placed in the gate-keeping role have an obligation to help licensing authorities assure that physicians who choose to discuss the medical use of cannabis and cannabis-based products with patients:

- Adhere to the established professional tenets of proper patient care, including
  - History and good faith examination of the patient;
  - Development of a treatment plan with objectives;

- Provision of informed consent<sup>50</sup>, including discussion of risks, side effects, and potential benefits;
  - Periodic review of the treatment’s efficacy;
  - Consultation, as necessary; and
  - Proper record keeping that supports the decision to recommend the use of cannabis
- Have a *bona fide* physician-patient relationship with the patient, i.e., should have a pre-existing and ongoing relationship with the patient as a treating physician<sup>51</sup>;
  - Ensure that the issuance of “recommendations” is not a disproportionately large (or even exclusive) aspect of their practice;
  - Not issue a recommendation unless the physician has adequate information regarding the composition and dose of the cannabis product;
  - Have adequate training in identifying substance abuse and addiction<sup>52</sup>.

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<sup>50</sup> If a physician recommends the use of cannabis for a minor, parents and/or legal guardians must be fully informed of the potential risks and benefits of such use and must consent to that use.

<sup>51</sup> This provision may be modified if the prescribing physician is a *bona fide* consultant brought into the care of a patient by the physician with whom the patient has a relationship. This further defines how to view and evaluate the actions of the physician who holds her/himself out as an expert in cannabis medical care who has no connection to the primary physician of the patient for whom crude cannabis is recommended.

<sup>52</sup> This is particularly germane to the ASAM which consists of physicians knowledgeable in drug abuse and addiction and who advocate to ensure that all physicians have the knowledge to manage CNS medications responsibly in the general patient population and can identify and treat or refer for treatment cases of abuse and dependence to psychoactive substances.

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