Marijuana Dispensaries and the Federal Government: Recommendations to the Obama Administration 2009: Part 1
Andrea G. Barthwell, M.D.

Abstract
Cannabis dispensaries are proliferating at a rapid rate — a cause for concern, given the potential for such operations to take advantage of desperate patients and put seriously ill patients at affirmative risk. Local jurisdictions do not have sufficient resources to deal with these abuses. Requiring the DEA unequivocally to take a “hands-off” approach, no matter how egregious the dispensary’s practices, will not serve the best interests of patients.

Definitions
The terms “cannabis” and “marijuana” are used interchangeably in this paper to refer to the psychoactive material, in either herbal or resinous form, from the Cannabis genus of flowering plants.

The use of the terms “medical marijuana” and “medical marijuana dispensaries” in this paper should not be taken as conferring or acknowledging any validity to the use or distribution of cannabis for medical purposes.

I. Introduction
In the early weeks of his administration, President Barack Obama has voiced a number of laudable goals. He has stressed that “Science and the scientific process must inform and guide decisions of my Administration on a wide range of issues…”(1) He has expressed compassion for seriously ill patients and their families. (2) With regard to the use of marijuana for medical purposes, the president is said to believe that “federal resources should not be used to circumvent state laws.” (3) Prior to his election, then-Senator Obama noted that any use of marijuana for medical circumstances should take place “under strict guidelines… in the same way that other [pain relievers] or palliative drugs would be prescribed.” (4) These aspirations are not necessarily inconsistent. As this paper will show, each of these goals can be met without allowing marijuana dispensaries to multiply free of federal control and intervention.

The Administration need not fear that Drug Enforcement Agency (DEA) intervention into cannabis dispensaries will conflict with state law; indeed, dispensaries are, in almost all instances, not permitted by state medical marijuana laws. Nevertheless, cannabis dispensaries are proliferating at a rapid rate — a cause for concern, given the potential for such operations to take advantage of desperate patients and put seriously ill patients at affirmative risk. Local jurisdictions do not have sufficient resources to deal with these abuses. Requiring the DEA unequivocally to take a “hands-off” approach, no matter how egregious the dispensary’s practices, will not serve the best interests of patients.

Uncontrolled proliferation of these dispensaries will seriously undercut our Food and Drug Administration (FDA) drug approval system and deprive patients of important regulatory protections. Such a result will defeat the Administration’s avowed desire to support and follow the results of sound science. As President Obama has stressed, medical marijuana should be controlled “the same … as other drugs prescribed by doctors.” Other prescription medications, such as morphine, are subject to a host of quality, safety, and efficacy requirements. Without such requirements, vulnerable patients can be exposed to harmful or ineffective products.

The Food, Drug, and Cosmetic Act (FDCA) and the Controlled Substances Act (CSA) are carefully integrated to ensure that patients’ access to medications is determined by good medical science, not politics. The FDA approves specific medical products for marketing and, thereafter, for distribution to patients, based on a determination of those products’ safety and effectiveness. Through the scheduling process, the DEA -- after a scientific and medical evaluation by the Department of Health and Human Services (the FDA, in particular) -- determines whether and which restrictions should be placed on basic classes of substances that may have abuse liability. Under this coordinated system, only individual products that have undergone rigorous scientific testing can be made available for medical use; crude botanical substances, such as opium, coca, and cannabis, cannot be sold to patients. Cannabis dispensaries, by distributing herbal cannabis and unapproved cannabis preparations directly to patients, significantly undermine this system.

In addition to maintaining the integrity of our domestic drug approval system, the United States must uphold its international treaty obligations. Under the Single Convention on Narcotic Drugs, which governs the cultivation, distribution, and use of marijuana, the U.S. must prohibit or strictly regulate such activities. When Congress enacted the CSA -- which is enforced by the DEA -- it expressly recognized our obligation to adhere to this and other drug control treaties. Again, the scientific process should guide our path as we fulfill our global responsibilities. The Administration should therefore allow the DEA to determine when, and to what extent, federal
The legal status and common practices of cannabis dispensaries

Most Cannabis Dispensaries are Illegal Under State Medical Marijuana Laws.

The DEA’s intervention into the practices of marijuana dispensaries does not circumvent state law or violate the concept of “states’ rights.” First, state legislation relating to the use of cannabis for medical purposes is generally quite limited in scope. These laws merely qualify the reach of the state’s existing criminal legislation prohibiting the use, possession, cultivation, etc., of cannabis.(5) California’s medical marijuana law -- the oldest in the nation -- clearly illustrates this fact. Proposition 215, the California Compassionate Use Act of 1996 (CCUA), (6) was enacted by the voters in 1996. The Act renders possession and cultivation of cannabis noncriminal under specified conditions; that is, it creates a potential defense against criminal prosecution and conviction. (7) The California Supreme Court has specifically ruled that the Act confers only a limited immunity which “operates by decriminalizing conduct that otherwise would be criminal.”(8) Such enactments do not fall within the realm of classic “states’ rights.”(9)

Second, in most cases, cannabis dispensaries are not actually authorized under these state medical marijuana laws. In California, for example, the original CCUA decriminalized the cultivation and possession of cannabis by a patient, or by that patient’s “primary caregiver,” if the use of cannabis was recommended by the patient’s physician. A primary caregiver was defined as the individual designated by the patient who has consistently assumed responsibility for the patient’s housing, health, or safety. The California Supreme Court has ruled that a person whose responsibilities consist principally of supplying cannabis and instructing on its use, and who otherwise only sporadically takes a patient to medical appointments, cannot qualify as a primary caregiver under the CCUA.(10) The Court concluded that a primary caregiver must prove at a minimum that he or she consistently provided caregiving, independent of any assistance in taking medical marijuana, at or before the time he or she assumed responsibility for assisting with medical marijuana. A primary caregiver must be the principal, lead, or central person responsible for rendering assistance in the provision of daily life necessities.

In 2003, the California state legislature enacted the Medical Marijuana Program (MMP).(11) The MMP clarified, but did not modify or expand, the reach of the CCUA.(12) The MMP acknowledges that patients and their primary caregivers may “associate” in order to cultivate cannabis “cooperatively or collectively” for medical purposes, without becoming subject to criminal sanctions solely because of that fact.

This language does not establish a “green light” for cannabis dispensaries. The California Attorney General has recognized that this provision was intended to be quite narrow. In August 2008, the State Attorney General issued guidelines to identify legitimate cooperatives and collectives.(13) The guidelines stressed that neither cooperatives nor collectives should purchase cannabis from, or sell to, non-members; instead, “they should only provide a means for facilitating or coordinating transactions between members.” Both types of entities must carefully monitor their members, and both should document “each member’s contribution of labor, resources, or money,”(14) as well as tracking and recording the source of the cannabis. Neither type of entity should profit from the sale or distribution of cannabis.

These guidelines allow for small groups of patients and primary caregivers to share the labor, expenses, and other responsibilities of cultivation on a common piece of land or other facility. This description does not apply to the vast majority of cannabis dispensaries in California, which have hundreds or even thousands of members.

In California, dispensaries have had 13 years to flourish, and it is in California that their abuses have become evident. Most dispensaries are merely retail storefronts that distribute cannabis to customers. The California Attorney General has made clear that such dispensaries are operating outside the boundaries of state law: “dispensaries that merely require a patient to complete a form summarily designating the business owner as their primary caregiver – and then offering cannabis in exchange for cash “donation” -- are likely unlawful.”(15) Nevertheless, dispensaries have proliferated across California.(16)

It is the current system and practices of medical marijuana dispensaries in California, and not the DEA’s disruption of their merchandising operations, that circumvent state law, both medical marijuana laws, and laws prohibiting the sale or possession of cannabis for non-medical purposes.

The Operation of Cannabis Dispensaries Will Not Generate Scientific Data Leading to a Meaningful Assessment of Cannabis-based Medications.

The practices of cannabis dispensaries will not enable this country to answer the pivotal question: what are the scientific data which demonstrate the risks and benefits of cannabis or cannabis-derived medications? Without such data, no new medical product can gain acceptance by the medical profession, policymakers, and an informed public. California’s cannabis dispensaries offer a broad menu of cannabis products to a wide and shifting range of customers. Different strains of herbal materials, as well as capsules, highly concentrated extracts, and edibles are available. Herbal material may be smoked or otherwise inhaled by means of a wide variety of devices. Patients may try one product (or one dispensary), then another. Some patients will have adverse reactions, or will obtain no benefit. Those individuals will simply not make further purchases; their experiences will not be recorded or otherwise captured for medical benefit/risk analysis.

Such practices cannot generate reliable, controlled data that could lead to a meaningful assessment of the future of cannabis or cannabis-based medical products—certainly not data on the myriad different cannabinoid preparations and dosage forms. Acceptable and usable scientific data can be generated only by transforming...
Cannabis Dispensaries May Put Seriously-Ill Patients at Risk.

State medical marijuana laws themselves recognize that cannabis is not a "harmless herb," akin to a dietary supplement or a home remedy. These laws treat cannabis more like a prescription medication, placing a licensed physician as the gatekeeper to a patient’s access to cannabis(17) (the physician, however, is not required to be federally registered, despite the fact that cannabis holds Schedule I status under the CSA). Despite this "quasi-prescription" status, there is little assurance of quality, consistency, safety, or efficacy. Cannabis in herbal form, or contained in crude preparations, is not a homogenous substance.(18) Depending on the concentration of various cannabinoids and other plant components, use of inert excipients, and delivery system or dosage form, patients may be exposed to a variety of active ingredients with quite different pharmacological effects.

Increasingly, cannabis cultivated in North America and Europe is being bred to express very high concentrations of tetrahydrocannabinol (THC).(19) By contrast, cannabidiol (CBD), a non-psychotoxic cannabinoid that dampens down the effects (including the psychoactive effects) of THC, and which is present in significant amounts in cannabis used centuries ago, has been bred out of modern cannabis.(20) The delivery system also enormously affects the impact that a cannabinoid product has on a patient. If inhaled (as in smoking or vaporizing), THC blood levels rise rapidly and then fall dramatically, which is likely to cause undesirable psychoactive side effects. Indeed, when smoked cannabis is compared with standardized cannabinoid-derived product (containing equal amounts of THC and CBD and delivered by a sublingual method), the patients using smoked cannabis report more significant adverse events.(21) In addition, a recent small study examining the effects of cannabis delivered in a (non-FDA-approved) vaporizer,(22) the subjects experienced notable intoxication; they found the cannabis with an intermediate THC concentration (3.4%) more tolerable than the higher THC concentration (6.8%) material.(23) Oral consumption has delayed and unpredictable effects.(24) This variability and unpredictability of effect may be particularly harmful to seriously ill patients, who are often debilitated and likely to be taking a range of other prescription medications.

Cannabis distributed by dispensaries also poses other, even more serious risks for patients. It may be contaminated by pesticides,(25) heavy metals, or fungus. For example, in the Netherlands, cannabis is grown for medical use by two cultivators who are licensed by the government’s Office of Medicinal Cannabis. The cannabis has such high microbial content that it must be irradiated before it can be distributed to patients.(26)

In a U.S. cannabis dispensary, however, there is no such quality control. If seriously ill patients suffer harm from such contamination,(27) they will receive no compensation, there will be no product recall or governmental investigation, and there is no tool to deter future malfeasance. In short, none of the federal and state regulatory protections are in place, and the cannabis distributed by dispensaries is not subject to reliable oversight.(28)

Cannabis Dispensaries May Take Advantage of Desperate Patients.

Reverend Scott Inman, one of the early California proponents of "medical marijuana," co-author of Proposition 215 and a founder of one of the original dispensaries, has voiced concern that dispensaries can be predatory, taking economic advantage of desperate and vulnerable patients:

We created Prop. 215 so that patients would not have to deal with black market profiteers. But today it is all about the money. Most of the dispensaries operating in California are little more than dope dealers with store fronts.(29)

There is little doubt as to why cannabis dispensaries are multiplying at such a rate. The price of cannabis in dispensaries ranges from $12.50 to $25 per gram (28 grams per ounce).30) The average "medical" user with a chronic medical condition may consume from 1.5 to 3.0 grams per day. Therefore, the monthly cost to patients ranges from $562 (1.5 grams/day at $12.50/gm) to $2,250 (3 grams/day at $25/gm). Since the herbal cannabis, which is of varying strains and quality, has not received FDA approval, none of this expense is covered by a patient’s health insurance,(32) and there is no assurance of quality control or accurate dosage information.

This system actually impedes access by patients to cannabis-derived medications. If a medication has gone through the FDA process, there is at least an opportunity for it to be covered by public or private health insurance. Given its exclusion from health insurance plans, its cost exceeds that which most seriously ill patients, many of whom may not be working, can afford to purchase. This cost in turn implies that the majority of purchasers are not, in fact, patients who require cannabis for medical purposes. In the meantime, cannabis dispensaries are profiting; some dispensaries take in over $20,000 per day. (33)

The need for regulatory protections.

Allowing a Proliferation of Cannabis Dispensaries Will Seriously Undercut the FDA Drug Approval System and Deprive Patients of Important Regulatory Protections.

President Obama has expressed his desire to ensure that the U.S. provides "continued global leadership in scientific discoveries and technological breakthroughs." He has assured the public that modern scientific developments will "guide" the Administration's policy decisions. A proliferation of cannabis dispensaries in states across the country would have the opposite effect, seriously undermining the FDA approval system. The federal Food, Drug, and Cosmetic Act (FDCA) and the federal Controlled Substances Act (CSA) work in synergy to form this impressive regulatory fabric. The FDCA requires that rigorous scientific data determine which medications may enter the marketplace and, thereafter, be prescribed and distributed to patients. The CSA
establishes a process (scheduling) through which those scientific data can be used to ensure that controlled substances are made available for -- and limited to -- appropriate medical and scientific use, through a closed system of distribution that includes proper registration, security, recordkeeping, reporting, quota, and other requirements.

The Requirements of the Food, Drug, and Cosmetic Act Reduce the Likelihood that Patients Will be Exposed to Harmful or Ineffective Products.

The FDCA has been developed over more than a century to protect the health and safety of vulnerable patients. It enforces rigorous standards at all stages in the development of a new medicine.(37)

Before a medical product may be approved by the FDA and be released for marketing, it must be assessed in various nonclinical and preclinical laboratory tests, including drug-drug and drug-food interaction tests. Its final formulation must be analyzed for batch consistency, stability, and absence of dangerous contaminants. Its manufacturing process must be validated and quality-controlled.

Even after extensive preclinical studies have demonstrated the likely safety of the product for human use, several phases of clinical (human) research must be conducted. If a product is intended to be used for a chronic condition, carcinogenicity and reproductive toxicity tests must be performed. Adverse events must be reported and described in the product label. The research is published in peer-reviewed journals, enabling physicians to judge the quality of the research, as well as the relative safety and efficacy of the product.

The FDA also inspects and supervises the pharmaceutical manufacturer's facility. If a flaw exists in the manufacturing process, the FDA can withhold marketing approval. Subsequent to approval, if the FDA receives reports of serious, unrecognized side effects, a product's label can be amended to include heightened warnings, or the product can be removed from the market entirely.

This thorough and dynamic process reduces the likelihood that patients will be exposed to dangerous or ineffective products, and provides important data to allow physicians to conduct meaningful dialogues with, and give informed advice to, patients regarding treatment options.

The Controlled Substances Act Plays a Critical Role in Ensuring that Properly-Tested Medications are Made Available for Appropriate Medical Use.

The CSA and the Drug Enforcement Administration (DEA) play important roles in this system of medication development. When medications contain controlled substances, and therefore pose a potential risk of abuse or addiction, the regulatory system is even more cautious. Mere FDA approval of such a medication is not sufficient; the product must also undergo review through an administrative process under the CSA (the scheduling process).

Cannabis proponents often contend that herbal cannabis should be moved from Schedule I to Schedule II in order to increase its availability to patients through cannabis dispensaries. This argument, however, reflects a misunderstanding of the scheduling process as it relates to the ultimate FDA approval and marketing of a medication. That process must be viewed in the context of the larger FDA/DEA regulatory scheme.

When Congress enacted the CSA, it established five categories, known as schedules, to which different levels of requirements, restrictions, and prohibitions are attached.(38) A drug's classification in a specific schedule is determined by its abuse and dependence potentials on the one hand, and by the evidence of its safety and therapeutic effectiveness on the other. The scheduling process involves independent but complementary roles for the DEA, Department of Health and Human Services, the FDA, and the National Institute on Drug Abuse (NIDA) in particular.

Substances in both Schedules I(39) and II are subject to the greatest restrictions because they have a "high potential for abuse."(40) For the most part, these restrictions are similar: for example, bulk manufacturers of Schedule I or II substances are subject to production quotas,(41) manufacturers of finished dosage forms (products) containing Schedule I or II substances are subject to procurement quotas.(42) Because they have no "accepted medical use," Schedule I substances are subject to some additional restrictions and may only be used in FDA-approved research programs.(43)

Under the CSA, Schedule II Placement Does Not Make a Substance Available for Direct Use By Patients.

The CSA schedules contain basic types or "classes" of substances (such as oxycodone), not specific products (such as OxyContin® or Fentora®), although each new "branded" medication undergoes a scheduling analysis as part of the FDA approval process. Placement of a substance in Schedule II is not sufficient to allow a specific product containing the substance to be marketed and distributed directly to patients. The latter requires FDA approval.

In order for a substance to move from Schedule I to Schedule II, the DEA must determine that it has an "accepted medical use." In order for a substance to have an "accepted medical use," the following criteria must be met:

- Its chemistry must be known and reproducible;
- There must be adequate safety studies;
- There must be adequate and well-controlled studies proving efficacy;
- It must be accepted by qualified experts; and

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The scientific evidence must be widely available. (44)

These criteria can only be met by data of very high scientific quality, essentially equivalent to the data that must be generated in order for a specific finished product to achieve FDA approval. (45) As a practical matter, therefore, the scheduling of new controlled substances generally occurs only after, or simultaneously with, FDA approval of products containing those substances. (46, 47)

FDA Approval is Required in Order for a Specific, Finished Medication to be Marketed and Distributed to Patients.

By contrast to the CSA’s scheduling of substances rather than individual products, the FDA approves only specific products for marketing and distribution to patients. The FDA does not approve pure active pharmaceutical ingredients (APIs), nor crude herbal substances, such as narcotic raw materials (NRM). Only a finished dosage form containing a specific type of controlled substance can obtain FDA approval and become a prescription medication.

This applies to cannabis as well as to other controlled substance plant materials. In 1970, at the time it enacted the CSA, Congress placed opium and coca leaves in Schedule II of the CSA because modern, standardized, and refined medical products derived from these substances were already on the market. Such schedule II placement did not put crude opium or coca leaves on the pharmacy shelves. Opium and concentrate of poppy straw (CPS) (48) contain different concentrations of alkaloids, such as morphine, thebaine, and oripavine. These alkaloids are themselves considered Schedule II substances, from which final pharmaceutical products are developed. (49) If a dispensary were to attempt to cultivate and distribute crude opium or coca leaves, it is beyond doubt that the DEA would have both the authority and the obligation to take action against such conduct, whether or not that activity was decriminalized under state law.

Author Information
Andrea G. Barthwell, M.D.

Dr. Barthwell is a member of EMGlobal LLC, a firm that advises on public health policy. In the past, she has worked in an advisory capacity for GW Pharmaceuticals Limited and King Pharmaceuticals, Inc., on issues of public health nature.

Bio: Andrea Barthwell, M.D., F.A.S.A.M., is the former Chief Executive Officer of Human Resources Development Institute, Inc. (HRDI), a community-based behavioral health and human services organization. Dr. Barthwell served from 2002 to 2004 as Deputy Director for Demand Reduction of the Office of National Drug Control Policy, a President-appointed and Senate-confirmed position. She is a former president of the American Society of Addiction Medicine. Dr. Barthwell also is a former member of the National Institute on Drug Abuse and Center for Substance Abuse Treatment National Advisory Councils, as well as the U.S. Food and Drug Administration’s Drug Abuse Advisory Committee. She earned her undergraduate degree in Psychology from Wesleyan University in Connecticut and received her M.D. from the University of Michigan. Dr. Barthwell is a member of the global health care and consulting firm EMGlobal LLC.

Michael C. Barnes, Esq.
DCBA Law & Policy

Mr. Barnes is a member of DCBA Law & Policy, a firm that advises on public health policy. In the past, he has worked in an advisory capacity for Alpharma Inc. on issues of public health nature.

Bio: Mr. Barnes is responsible for strategic growth, business development, and client satisfaction for DCBA Law & Policy and its Center for Lawful Access and Abuse Deterrence (CLAAD). Prior to establishing DCBA in 2004, Mr. Barnes served as confidential counsel in the Office of National Drug Control Policy, where he provided direction on policy and program matters aimed at reducing the demand for illicit drugs. Leading up to his presidential appointment, Mr. Barnes worked for The Perlas Law Firm.

Mr. Barnes obtained his Juris Doctor degree from George Mason University School of Law. He earned a master’s degree in international economic policy from La Universidad de Belgrano in Buenos Aires, Argentina, where he lived and studied as a Rotary Foundation International Ambassadorial Scholar. He received his bachelor’s degree summa cum laude from Flagler College.

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References


7. People v. Mower 28 Cal.4th 457, 472; 122 Cal.Rptr.2d 326 (2002). It is not uncommon for a state to render certain conduct noncriminal that otherwise would be criminal under its laws. See, e.g., Calif. Penal Code sec. 602(n) (the crime of trespass on another's property is not applicable to persons engaged in lawful labor union activities); Calif. Insurance Code sec. 12924(b) ("no individual shall be prosecuted or be subjected to punishment for any crime concerning which he/she is compelled by the Insurance Commissioner to testify or produce other evidence").

8. People v. Mower, supra, at p. 473. This limited immunity entitles a defendant to raise a defense at trial and to bring a motion to set aside an indictment or information prior to trial. Id. at p. 470. It does not confer complete immunity from arrest and prosecution. Id. at p. 474.

9. Neither the CCUA nor, subsequently, its clarifying legislation, created other, affirmative "rights." For example, there is no requirement for any accommodation of the use of cannabis on the property or premises of any place of employment or during the hours of employment. See Calif. Health & Safety Code §11362.785(a). Furthermore, nothing precludes an employer from discharging an employee who fails a drug test as a result of his/her use of cannabis for medical purposes (even outside of working hours or the workplace). See Calif. Health & Safety Code §11362.785(a); Ross v. Ragingwire Telecommunications (2008) 442 Cal.4th 920, 70 Cal.Rptr.3d 382 (pre-employment drug testing). These provisions demonstrate that no robust "rights" are created by the limited grant of immunity.


12. Under California law, the legislature cannot amend an initiative, such as the CCUA, unless the initiative grants the legislature authority to do so, Calif. Const., art. II, §10, subd.(c). The CCUA does not give the legislature authority to amend it without voter approval.


14. "Members also may reimburse the collective or cooperative for marijuana that has been allocated to them. Any monetary reimbursement that members provide to the collective or cooperative should only be an amount necessary to cover overhead costs and operating expenses." Id.

15. Attorney General Guidelines at p. 11.


17. For example, patients cannot "self-diagnose," as they do when purchasing dietary supplements, nor can patients seek a physician's approval only after their use of cannabis, in an effort retroactively to "validate" such self-diagnosis. See, e.g., People v. Rigo (1999) 68 Cal.App.4th 409.

18. This is also true of opium. Different strains of the opium poppy may be rich in morphine, thebaine, or oripavine. These substances, in turn, are used to prepare very different medications. See DEA, "Authorized Sources of Narcotic Raw Materials," 73 Fed. Reg. 6843 (Feb. 6, 2008).


Cannabinoids as Therapeutics, (Basel, Switzerland; Birkhauser Verlag) (2005).


22. The Volcano® is produced by Storz & Bickel GmbH & Co. in Germany. A description and drawing can be found in Abrams, D., infra. It has limited portability. In use outside the clinical trial setting, the dose of cannabinoids, and the extent of pyrolytic products, will vary with the temperature setting and the patient's inhalation practices.


25. There is no requirement in local legislation that cannabis sold in dispensaries must be organic. Indeed, one dispensary in San Francisco advertises itself as the "only" dispensary offering organic cannabis in the City. http://www.sforganiccannabisclubs.com/directory/san-francisco-alternative-patient-caregivers.htm.


27. One scientist has stressed that 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. See Hazekamp, supra, at p. 6.


32. In California, for example, state law does not require a government, private, or any other health insurance provider or health care service plan to be liable for any claim for reimbursement for the use of medicinal cannabis. Calif. Health & Safety Code §11362.785(d).


37. Even at the research stage, an investigational product may be tested in actual patients only if the physician-investigator has preliminary evidence of safety and a protocol approved by the FDA. The protocol must undergo careful scrutiny from an Institutional Review Board (IRB).

38. Congress placed most of these substances in their respective schedules as part of the CSA's enactment in 1970, but new substances are continually scheduled and existing substances are moved between schedules as new scientific data become available. DEA, "Controlled Substance Schedules," (Chronological Order). http://www.deadiversion.usdoj.gov/schedules/schedules.htm.

39. Examples of Schedule I botanical materials classified as "hallucinogens" are marijuana (cannabis), psilocybin, and ibogaines. Pure synthetic THC is also in Schedule I. 21 C.F.R. §1308.11.
40. A drug's potential for abuse is a threshold issue in determining the schedule into which the drug may be placed. The term is not defined in the CSA, but the legislative history demonstrates that the following factors are indicators that a drug or other substance has a potential for abuse:

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

Of course, evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.


41. 21 C.F.R. §1303.21; the registration application of a bulk manufacturer must pass through a notice (publication in the Federal Register) and comment procedure. 21 C.F.R. §1301.33.

42. 21 C.F.R. §1303.12.

43. Substances in Schedule II-V have an accepted medical use. Substances in schedules III-V also have lower abuse potential and are subject to fewer restrictions. Interestingly, in California, cannabis remains in Schedule I of the state controlled substances law, despite the fact that it has been decriminalized for limited medical use. Calif. Health & Safety Code §11054(d)(13).


45. Hence, FDA approval of a specific finished product is generally sufficient to establish an "accepted medical use" for the substance contained therein. There are rare exceptions. See, e.g., "dronabinol (synthetic) in sesame oil and encapsulated in a soft gelatin capsule in a U.S. Food and Drug Administration approved product" is in Schedule III and has a Drug Code of 7369, 21 C.F.R. §1308.13(g), whereas pure synthetic THC remains in Schedule I, with a Drug Code of 7370, 21 C.F.R. §1308.11(d). See, 51 Fed. Reg. 1746 (May 13, 1986); 64 Fed. Reg. 35928 (July 2, 1999) (dronabinol product). FDA-approved products containing GHB are in Schedule III while "street" GHB is in Schedule I. 65 Fed. Reg. 13235 (March 13, 2000). Pub. L. 106-172 (GHB). Hence, a formulated cannabis-derived product could be placed in Schedule II or III after FDA approval, while crude herbal cannabis could remain in Schedule I.

46. FDA approval is not technically a legal precondition to rescheduling. Grinspoon, supra, at p. 8991.

47. See, e.g., tapentadol. The finished pharmaceutical product, manufactured by Johnson & Johnson, was approved by the FDA in November 2008. DEA has issued a proposed rule placing tapentadol into Schedule II. 74 Fed. Reg. 7386 (Feb. 17, 2009). The finished product does not yet have a trade, i.e., "branded," name.

48. Under the CPS method (used by all cultivating countries except India), the plant is allowed to go to seed; portions of the plant are then processed into a concentrate. It is generally believed that CPS is less divertible than opium. CPS may be rich in morphine, thebaines, or oripavine. See DEA, "Authorized Sources of Narcotic Raw Materials," 73 Fed. Reg. 6843 (Feb. 6, 2009).

49. Thebaines is used to manufacture oxycodone, which in turn can be used to manufacture hydromorphone; oripavine is used to make buprenorphine, as well as naloxone (an opioid antagonist). Id. See 72 Fed. Reg. 54206 (Sept. 24, 2007) (oripavine scheduled separately in Schedule II - rather than as a derivative of thebaine - to comply with the U.S. 's obligations under the Single Convention).
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The Scientific Process

Crude Herbal Cannabis and Unstandardized Cannabis Preparations Do Not Meet the Standards of
Modern Medicine.

The Institute of Medicine (IOM) has recognized that crude herbal cannabis has little future as a true medication:

Although marijuana smoked delivers THC and other cannabinoids to the body, it also delivers harmful substances,
including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active
cannabinoids and canavolacids that are not expected to provide a precisely defined drug effect. For these reasons there is little
future in smoked marijuana as a medically approved medication. If there is any future in cannabinoid drugs, it lies
with agents of more certain, not less certain, composition.(50)

The IOM stressed that “the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a
licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid
delivery systems.”(51)

The FDA agrees that crude herbal cannabis is not a medication.(52) The California Medical Association recently
announced its intention to “re-examine the need for continued research on smoked herbal cannabis in light of
recent research on its benefits and harm and the long-term prospect of smoked herbal cannabis as a
medicine.”(53) The DEA also acknowledges the need for standardized product

[I-herbal cannabis should comprise only the starting material from which a bona fide medical product is ultimately
derived... [S]tandardizing herbal starting material represents only the first of many steps necessary to create a
modern medicine that is safe and effective for use in specific medical conditions... [A] final medical product...
must also be delivered in a dosage form that is consistent in composition and that allows the patient to obtain an
identifiable and reliable amount of medication.(54)

Only Recently Has Technology Made Possible the Development of Modern Cannabis-derived and
Cannabinoid Medications.

There are good reasons why the development of cannabis-derived medications has lagged far behind that of
synthetic and naturally-derived opioids and other modern medications. Given that the active ingredients (morphine,
codeine) of opium are water soluble, it was relatively simple in the 19th and early 20th centuries to isolate them and
develop standardized and purified medications with the technologies that existed at that time.(55)

The story of cannabis is quite different. Cannabinoids (especially THC) are lipophilic (i.e., not water soluble) and
unstable, making it difficult for early scientists to identify and isolate the active ingredients. Consequently,
potentially therapeutic applications were limited to oral preparation of cannabis (tinctures and extracts),(56) which
could not be adequately standardized. Patient response was variable and unpredictable. As more modern
medicines became available, these unreliable extracts and tinctures fell out of favor with the medical
profession.(57)

The modern era of cannabinoid research was in its infancy in 1964, when the primary psychoactive ingredient of
cannabis, THC, was isolated and then synthesized.(58) Beginning in 1969, a robust body of cannabinoid research
began to develop, following scientists’ discovery of the human cannabinoid receptor system.(59) This delay in the
development of modern cannabinoid and cannabis-derived medications has, therefore, been caused more by past
 technological limitations, than by governmental obstructionism. That development gap is now slowly closing, and
there is no justification for affording a non-scientific acceleration, i.e., a “free pass,” to herbal cannabis:

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 specific or selectively active pure compounds that permit more precise dosage and reduced
risk of unwanted side effects.(60)

This is not to say that complex botanically-derived preparations cannot pass FDA muster. There is strong evidence
that some properly tested and standardized plant preparations, including those derived from cannabis, may offer
different -- and better -- pharmacological effects than a pure, synthesized cannabinoid alone.(61)

The FDA has recognized that there is burgeoning scientific and public interest in botanically-based products, and
that modern technology makes it possible to develop medications of botanical origin. In order to guide the
development of such products, the agency has set forth the criteria that must be met to achieve FDA approval.(62) While allowing some flexibility at the early stages of medication development, the guidance specifically states that, by the time of Phase 3 clinical studies, the requirements for a botanical drug product are virtually the same as those that apply to a new chemical entity (NCE). Botanical Raw Material (BRT), such as herbal cannabis, has not been formulated, incorporated into a specific dosage form, and tested through this demanding NCE process. The FDA guidelines make it quite clear that, even if crude herbal cannabis were moved to Schedule II, it could not thereby be marketed and distributed directly to patients.

The Administration Should Respect and Support the Proper Workings of the Scientific Process.
As a result of modern technologies, and as demonstrated by the receptor research mentioned above, there is significant interest within the scientific and medical communities in cannabinoid research. Scientists are moving as expeditiously as possible to bring new cannabinoid products to market. Time is required, however, for such research to be conducted in accordance with modern medical standards. In keeping with its commitment to science, this Administration should do nothing to discourage these efforts. As President Obama has stated:

Medical miracles do not happen simply by accident. They result from painstaking and costly research, from years of lonely trial and error, much of which never bears fruit, and from a government willing to support that work.(64)

The United States is, indeed, supporting such work in this area. For example, the FDA has allowed a cannabis-derived product to enter into advanced clinical trials in the U.S. For the past ten years, research has been underway in the United Kingdom by GW Pharmaceuticals to develop a range of prescription medications derived from the components of the cannabis plant. (65) GW cultivates particular strains of cannabis that have been bred to express specific ratios of cannabinoids. In order to maintain the consistency of the plants' chemical composition, they are grown by clones (cuttings) under highly-standardized and computer-controlled conditions in secure glasshouses. GW extracts the pharmacologically-active components of the plant, removes waxes and other unwanted constituents, and formulates the resultant botanical drug substance into a final dosage form of specified composition, which is characterized by various standard chromatographic techniques.

The company's lead product, Sativex®, is an oromucosal (inside of the mouth) spray composed primarily of THC and CBD. It is believed that this combination has distinct and important pharmacological activity. The product has already been approved in Canada for neuropathic pain in multiple sclerosis and for cancer pain. The DEA has licensed the importer(66) and the research sites.

A number of other companies, including Alexza Pharmaceuticals, Inc. (THC aerosol product); Aphios (naturally-derived THC product); and Insys Therapeutics, Inc., are also developing cannabinoid products in the U.S. (67) All of these research programs are moving through the conventional domestic regulatory process. (68) None is attempting to distribute crude herbal cannabis, or non-standardized botanical preparations, to pharmacies and patients. (69) These research programs indicate that cannabis-derived medications can, and therefore should, be developed within the parameters of modern regulatory oversight. Allowing a proliferation of cannabis dispensaries would undermine these efforts to bring properly tested medications to market, a result at odds with this Administration's position that its policies should be based on sound science. (70)

Developing properly standardized and tested cannabis-derived or cannabinoid medications is not an easy matter; it requires patience, perseverance, and a commitment of substantial resources. But numerous medical tragedies(71) have proven that shortcuts to the FDA process do a disservice to patient safety and well-being. The FDA drug approval process is not perfect, as demonstrated by recent news about previously-unknown dangers of marketed medications, such as Vioxx®. (72) The lesson of these experiences, however, is not that we should do less testing, or lower our current standards, for prescription medicines. Indeed, those incidents have led to demands for greater oversight by the FDA and, recently, for the establishment of an independent institute to examine the comparative safety and effectiveness of medications. (73)

The FDA Has Limited Power to Protect Patients Who Seek Medical Treatment and Advice From Cannabis Dispensaries.
The FDA has limited jurisdiction to address the dangers posed by cannabis dispensaries. The provisions of the FDCA govern only products that have been introduced into interstate commerce. Therefore, it can be argued that the activities of intra-state cannabis dispensary operations are beyond the reach of the FDA. Ironically, the FDA has greater power over dietary supplements (which have generally passed through interstate commerce) and over health food stores than it does over cannabis dispensaries and their operators. (74) Indeed, the manufacturers of herbs and other dietary supplements (and the retail establishments that sell them) are prohibited by federal law from making claims regarding the product's medical usefulness or specific health effects. (75) Cannabis dispensaries, however, do give out advice, and provide books and pamphlets, containing such medical claims. (76)

The DEA, therefore, plays a critical part in protecting patients from dangerous, ineffective, and federally unapproved cannabis products. The CSA, and therefore the DEA's authority, extends to products containing controlled substances and activities that may affect interstate commerce, even if the specific products have been manufactured and distributed solely within the state. (77) If this Administration ties the DEA's hands with regard to dispensaries, patients will lose altogether any avenue of federal protection.

States Laws and Regulatory Bodies Should Enhance, Rather Than Undermine, the Protections Provided by the FDA System.
In cases other than medical marijuana, the FDA and DEA are able to rely to a large extent on state regulatory and law enforcement systems to support and augment the federal structures. States have generally accepted this
responsibility, enacting their own food and drug laws to fill the gap in the FDA's jurisdiction. These state laws are, for the most part, modeled after the federal FDCA. In California, for example, the Sherman Food, Drug, and Cosmetic Law ("Sherman Law") establishes rigorous scientific standards that must be met before a new drug may be marketed for medical use. The Sherman Law states that a new drug generally may not be sold, delivered, or given away unless a new drug application has been filed with, and approved by, the state or federal government.\(78\)

State regulatory boards and agencies similarly enhance the effectiveness of the FDA and DEA. State boards of medicine, nursing, pharmacy, etc., supervise the education, training, and practices of all health care providers who examine or advise patients, or dispense or distribute medications. Health care providers who do not adhere to accepted standards of medical practice may incur sanctions from these boards, as well as risk potential civil liability for inappropriate prescribing or other conduct falling below the standard of care.\(79\) Health care facilities are monitored and licensed by state departments of health services. State tort systems allow patients who have suffered injury from a medication to seek damages from the manufacturer, even if that medication has been FDA-approved.\(80\) These state mechanisms, when they operate effectively, provide patients with additional or greater avenues of redress and protection and, thereby, complement federal food and drug provisions.

By contrast, when states utilize their food and drug laws (or enact other state legislation) for the purpose of circumventing the FDCA, patient health and safety is jeopardized. In many ways, the current cannabis controversy parallels the Laetrile controversy of the 1970s. At that time, Laetrile (amygdalin) was vigorously promoted as a cancer treatment and preventative. Despite efforts by its supporters to characterize it as a dietary supplement ("Vitamin B17"), the FDA determined that Laetrile was a new drug (since it was intended for medical use) and was subject to premarketing approval.\(81\) Since it had not been proven safe and effective for medical use, the FDCA precluded Laetrile's shipment in interstate commerce. Desperate cancer patients, spurred on by anecdotal reports of efficacy, contended that they had a right to use Laetrile, despite evidence of cyanide toxicity. Laetrile advocates claimed that the FDA, the American Medical Association, the American Cancer Society, the pharmaceutical companies, and others were conspiring against Laetrile.\(82\) This political pressure, rather than scientific evidence, caused twenty-seven state legislatures to pass laws allowing the sale and use of Laetrile within their borders. These state laws had little effect, since it was not feasible to manufacture Laetrile within each state. "Propagators hoped, however, that if enough states legalized its use within the states, Congress would change the federal law as well."\(83\) Ultimately, the National Cancer Institute conducted clinical testing and determined that Laetrile was not effective as a cancer treatment.\(84\) The lesson of Laetrile is that state legislation should only be used to enhance, rather than undermine, the protections of the federal regulatory system.

The same is true with regard to controlled substances. Many states have adopted the Uniform Controlled Substances Act,\(85\) the provisions of which parallel those of the federal CSA. States can serve as an early warning system, and have the flexibility to respond more quickly to abuses of controlled substances -- or of uncontrolled substances with abuse potential -- within their borders.\(86\) For example, as an added layer of protection, states may require that individuals who conduct research into controlled substances must be independently inspected, licensed, and/or approved by state agencies, in addition to obtaining DEA registrations.\(87\) States may enact prescription monitoring programs to track physicians who prescribe controlled substances, in order to identify and stop inappropriate prescribing practices by physicians, as well as "doctor shopping" by patients (obtaining prescriptions from multiple doctors simultaneously).\(88\) States also have greater flexibility in their scheduling actions, if a state believes that a new substance has abuse potential and poses a threat to patient safety or public health, the state need not wait on the DEA; it may schedule that substance more restrictively, or prohibit its sale and use altogether.

Cannabis Dispensaries Are Not Subject to State Laws and Regulations Applicable to Entities Operating in the Health Care Area.

Cannabis dispensaries starkly conflict with this robust state system of patient-oriented controls. "Pot docs," for cash payments of several hundred dollars, provide recommendations to patients (including minors), with whom they have virtually no physician-patient relationship, to enable them to use cannabis for a wide variety of medical conditions.\(89\) Patients purchase cannabis from dispensaries with which they have only a retailer-consumer relationship. Dispensary personnel need not be licensed as health care providers, nor are they required to follow proper sterile techniques to protect against on-site bacteria\(90\) or other contamination of the herbal material, although it is intended for consumption directly by patients.\(91\) Despite their lack of training and accreditation, such personnel freely offer medical information and advice to patients\(92\) about the paralogy of cannabis products, including extracts, capsules, tablets, and various types of edibles. Some of these products can reach THC concentrations as high as 80%, which could produce significant side effects, especially in seriously ill patients or those who have not used cannabis before.\(93\)

At best, cannabis dispensaries are regulated at the local level.\(94\) Where they are permitted by local legislation (as in San Francisco),\(95\) such dispensaries are not regulated as if they were health care facilities (e.g., clinics or pharmacies) answerable to the state department of health services. Nor are the employees who provide direct patient service (e.g., distributing medical marijuana or medical advice) subject to the scope of practice restrictions and requirements supervised by the state boards of pharmacy, nursing, and medicine. Rather, dispensaries are regulated as if they were retail establishments, subject only to the Building, Planning, Housing, Police, Fire, and Health codes of the local jurisdiction.\(96\)

Cannabis and Cannabis-Derived Products Should Be Governed by the Quality Control and Other Testing Procedures Applicable to All Modern Medications.

Gradually, even some cannabis dispensaries have begun to voice concern that these unregulated distribution

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practices may be placing patients in danger. One operator has acknowledged that, if cannabis "is going to become an accepted mainstream medicine," there must be quality assurance and dosage information:

[A] dog walks in the grow room, and wags its tail—anything can be coming off that dog's tail. It's gross. Fertilizers with E. coli. Compost... they don't make right, anaerobic tea that has elevated levels of E. coli and salmonella. It has to come. There's no way that this is sustainable. All it takes is one story of immune-compromised people dying from Aspergillus infection.(97)

This operator has affiliated with an informal laboratory, and envisions a testing program using such instruments as a gas chromatograph and mass spectrometer.(98) He also notes, however, that "It's expensive to test every single thing that comes through the door—that's the price you pay with a decentralized supply system... five pounds coming from here and two from there."(99) It is far from certain whether other dispensaries would voluntarily join such an effort.

These rudimentary laboratory-testing efforts merely confirm the importance of adhering to the existing body of technological tools and methodologies mandated by state and federal regulatory agencies. There is no need to "recreate the wheel" for cannabis or cannabis-derived preparations. Drug manufacturers are already required to institute extensive testing procedures to ensure that their products are quality-controlled during manufacture, and that their formulations and dosage forms are standardized and reproducible. Testing procedures must be validated, instruments must be calibrated, equipment operators must be appropriately educated and trained, careful records must be kept, and practices must be sterile. Finished medical products must be analyzed for batch-to-batch consistency, and any degradants and minor contaminants must be identified and strictly limited.

Should a system of cannabis-testing laboratories ultimately develop at all, it is hard to imagine that it would be allowed to operate at a different or inferior level to the current U.S. medication-development system. If cannabis dispensaries are allowed to proliferate across the country, our current regulatory system, to which the American Medical Association and all other major U.S. medical associations give their unavailing support, may be seriously undermined.

If there were only a single state with a few dispensaries, the risk might not be as significant. At present, however, 13 states have laws declassifying the use of cannabis for medical purposes, and bills are pending in many more states.(100) If such cultivation and distribution activities are deemed to be beyond the reach of the DEA, dispensaries are likely to emerge all over the country.(101)

The United States' International Obligations

Good Science Should Also Guide Decisions Implementing Our Obligations Under International Drug Control Treaties.

President Obama has announced his intention to trust science and research when designing our international, as well as domestic, policies. Sound science should inform and guide this Administration as it implements our international responsibilities in the field of drug control policy. The U.S. -- and thereby the Department of Justice -- has an obligation under our international drug control treaties to control strictly the manufacture and distribution of controlled substances, including the cultivation and distribution of cannabis, within our borders.

In particular, if the U.S. permits the cultivation of cannabis plants for medical use, it must apply the same provisions as are imposed for the cultivation of the opium poppy for medical use. This rigorous system of controls must be maintained by a single government agency. States, therefore, cannot have sole jurisdiction over the proliferation of cannabis dispensaries.

The United States is a signatory to the Single Convention on Narcotic Drugs 1961 ("Single Convention").(102) This treaty was intended to ensure that the production and use of narcotic substances are limited exclusively to bona fide medical and scientific purposes.(103) Accordingly, the Single Convention requires a party to impose strict controls, not merely on international trade, but also on domestic manufacture, distribution, import, export, and possession of botanically-derived controlled substances (such as coca, opium, and cannabis).

The phrase "medical and scientific purposes" has a clear meaning. The treaty was promulgated at a time when governments around the world were developing regulatory procedures to ensure the quality and safety of medical products.(104) Crude narcotic plant material was not considered suitable for direct medical use. For example, under the treaty, opium smoking was not an accepted method for delivering the therapeutically useful components contained within the herbal material.(105)

The Single Convention recognized that different countries may have different regulatory systems.(106) However, the treaty expected that each party would in good faith adhere to modern scientific standards: that is, employ conventional regulatory standards when determining whether, when, and which, narcotic substances and products could be made available for medical use. Nowhere in the treaty is there any suggestion that a Party may allow a diluted or informal medical system solely for a specific controlled substance such as cannabis.

In response to the activities of medical cannabis proponents, the International Narcotics Control Board (INCB)(107) stressed that a party may not allow cannabis to be cultivated, manufactured, and used for medical purposes unless such products have satisfied the rigorous regulatory standards that apply to other medical products. Such use must be supported by objective scientific data from properly-conducted research studies, and must otherwise accord with principles of modern medicine.(108)
The Single Convention places particularly severe restrictions on the cultivation of cannabis, opium, and coca bush. Article 23 requires that, if a party permits cultivation of opium poppies within its borders, the Party must establish and maintain a national Agency to carry out the Party's obligations. Articles 26 and 28 apply those requirements to the cultivation of the coca bush and the cannabis plant, respectively. Article 23 requires that only nationally-licensed cultivators, whose license specifically identifies the precise extent and location of the land that they are authorized to cultivate, may grow such narcotic plants.(110) They must deliver their total crops to the Agency, and only the national Agency may deal with such crops. The Agency must have the exclusive right of importing, exporting, wholesale trading, and maintaining stocks.(111)

The National Institute on Drug Abuse (NIDA) serves as the U.S. national Agency under the Single Convention.(112) Under the auspices of NIDA, the U.S. maintains a domestic cultivation facility, in which research-grade cannabis is cultivated by the National Center for Natural Products Research at the University of Mississippi under contract with NIDA.(113) This cannabis is supplied to investigators who have research protocols that have been approved by the FDA and by an expert committee of the Public Health Service, and who have obtained research registrations from the DEA.(114) As of April 2004, the University of Mississippi, with the approval of NIDA and the PHS committee,(115) had provided cannabis to more than 17 clinical and preclinical studies funded by the Center of Medicinal Cannabis Research (CMCR) at the University of California San Diego.(116)

If, in the future, cannabis-derived medications were to be developed and approved for marketing, it would not be necessary for the cannabis cultivation (production of starting materials) to take place in the United States. The herbal material, or the Botanical Drug Substance (extracts) could be imported into the U.S. for further formulation. For over 65 years, it has been the policy of the U.S. not to cultivate or produce narcotic raw material (NRM), such as opium, poppy straw, and concentrates of poppy straw (CPS).(117) By long-standing international policy, the U.S. is a country that imports and consumes, rather than one that produces and supplies, NRM.(118) The U.S. relies on a specific list of countries authorized to import NRM into the U.S. in order to meet the legitimate medical needs of the U.S.(119) This list is deliberately kept very short, in order to prevent a proliferation of NRM-producing countries.

Furthermore, the treaty imposes additional controls on all manufacture and distribution of cannabis-derived and other controlled substances. Such activities must be conducted by federally-licensed and regulated entities that are producing standardized products for medical or research purposes.(120) Therefore, were the U.S. to permit dispensaries in various states across the country to distribute(121) or cultivate cannabis for medical use, the U.S. would be in violation of these unmistakably clear treaty obligations. The INCB has confirmed this position:

The control measures applied in California for the cultivation, production and use of cannabis do not meet the control standards set in the 1961 Convention to prevent diversion of narcotic drugs for illicit use. Such standards require, inter alia, the control of cultivation and production of cannabis by a national cannabis agency, and detailed record keeping and reporting on the activities with cannabis, including reporting to INCB.(122)

The Controlled Substances Act Was Enacted in Part to Fulfill Our Obligations Under the Single Convention, and the Proliferation of Cannabis Dispensaries Cannot be Left Solely to State Control.

The federal-CSA was enacted, in part, to fulfill the United States’ obligations under the Single Convention.(123) The CSA and its implementing regulations have two prongs. They are designed:

1) to ensure that there is a sufficient supply of controlled substances for legitimate medical, scientific, research, and industrial purposes; and

2) to prohibit, deter, and punish the sale and use of controlled substances for illegal purposes.

These goals parallel those of the Single Convention: to ensure that narcotic and other psychoactive substances are manufactured, traded, and used only for legitimate (i.e., evidence-based) medical and scientific purposes. If the DEA were prohibited from shuttering cannabis dispensaries and seizing the materials purified therein, the U.S. would have failed to comply with its international responsibilities. If the U.S. does not abide by its treaty obligations, other countries will be unlikely to adhere to theirs. As in other arenas, the U.S. should seek to be a leader with respect to modern medical science and its responsibilities under international agreements.

The CSA achieves its purposes by:

1) establishing a process (scheduling) through which scientific and other data may be used to ensure appropriate levels of control of abuseable substances, and the adequate availability of medications containing them;(124) and

2) creating a "closed" system, in which every importer, exporter, manufacturer, distributor, dispenser, and researcher handling a controlled substance must meet strict licensing, recordkeeping, and security requirements, which are consistent with those required by the Single Convention.

Cannabis dispensaries operate entirely outside of this system of controls. It is hard to see the logic or merit of any position that would relieve cannabis dispensaries from federal oversight, despite the fact that cannabis is a Schedule 1 substance, while requiring manufacturers and distributors of Schedule II substances to secure DEA registrations, adhere to quotes, keep accurate records, and institute strict security measures. The DEA has both
the power(125) and the obligation to curb the proliferation of cannabis dispensaries. It cannot abdicate this responsibility in the name of deferring to states’ rights.(126)

Under the Single Convention, the United States must in good faith strive to prevent the non-medical sale and use of controlled substances. A decision by the Administration to prevent the DEA from intervening in cannabis dispensaries, if they are "authorized" under state law, will effectively prevent the agency from enforcing the CSA against cannabis retail storefronts that are merely subterfuges for non-medical distribution of cannabis.

State and local law enforcement do not alone possess adequate resources to stem the proliferation of dispensaries that distribute cannabis for non-medical use. Moreover, local law enforcement needs the assistance of the DEA in combating these operations. These entities do not have access to the highly efficient law enforcement tools that the DEA has at its disposal. For example, local law enforcement cannot utilize federal asset forfeiture laws to deter landlords from permitting cannabis distribution activities to take place on their property.(127) Indeed, attempting to require the DEA selectively to halt only non-medical distribution centers will require the DEA to dissipate its limited resources in a futile line-drawing exercise.

The process of identifying cannabis dispensaries that distribute cannabis for non-medical use would be extremely onerous for a federal agency. In order to fulfill its unquestioned obligation to enforce the CSA’s and Single Convention’s prohibitions against non-medical distribution, the DEA would be required to examine the records of dispensaries to make the following assessments: the true non-profit nature of the entity; the means by which physician recommendations are verified; the bona fides of members and the relative labor, monetary, or other resource contributions of those members to the non-profit enterprise; the source of the cannabis; and whether it can be determined to have been cultivated in all cases by legitimate members, etc.(128)

Moreover, the DEA’s resource-intensive struggle to distinguish between legitimate (under state law) and unlawful (under state law) dispensaries would be compounded by the fact that, increasingly, cannabis dispensaries have delivery services.(129) Such delivery services would make it even more difficult for the DEA to track and evaluate cannabis distribution activities for compliance with state law.

Even for local jurisdictions, detailed state guidelines, such as those issued by the California Attorney General, are difficult enough to interpret and enforce. To require the DEA to take a hands-off approach to any dispensary that may be operating in accordance with such state guidelines would effectively ban the DEA from any significant cannabis interdiction, leading to a free-for-all of cannabis dispensaries across the state and, potentially, across the nation. As a result, cannabis would become readily available for any use—both medical and recreational.(130)

Conclusion

For the reasons stated above, the Obama Administration must take a measured approach in addressing marijuana dispensaries, maintaining the commitment to enforcing the CSA that the Department of Justice has recently reiterated. This commitment must be met even in states that authorize "medical" use of marijuana, and especially where illegal distributors attempt to use state medical marijuana laws as a pretense. We recognize that the Department of Justice and the DEA have limited resources, and those resources must be spent wisely. The United States, however, also has both domestic and international responsibilities to protect the health and safety of patients and to promote the responsible development of modern medications. A fixed Administration ruling against DEA intervention into the operations of cannabis dispensaries would allow informal, quasi-medical networks to spring up across the nation, thereby putting at risk the critical protections so carefully crafted under the national food and drug legislation of the 20th and 21st centuries.

Author Information

Andrea G. Barthwell, M.D.

Dr. Barthwell is a member of EMGlobal LLC, a firm that advises on public health policy. In the past, she has worked in an advisory capacity for GW Pharmaceuticals Limited and King Pharmaceuticals, Inc., on issues of a public health nature.

Bio: Andrea Barthwell, M.D., F.A.S.A.M., is the former Chief Executive Officer of Human Resources Development Institute, Inc. (HRDI), a community-based behavioral health and human services organization. Dr. Barthwell served from 2002 to 2004 as Deputy Director for Demand Reduction of the Office of National Drug Control Policy, a President-appointed and Senate-confirmed position. She is a former president of the American Society of Addiction Medicine. Dr. Barthwell also is a former member of the National Institute on Drug Abuse and Center for Substance Abuse Treatment National Advisory Councils, as well as the U.S. Food and Drug Administration’s Drug Abuse Advisory Committee. She earned her undergraduate degree in Psychology from Wesleyan University in Connecticut and received her M.D. from the University of Michigan. Dr. Barthwell is a member of the global health care and consulting firm EMGlobal LLC.

Michael C. Barnes, Esq.

DCBA Law & Policy

Mr. Barnes is a member of DCBA Law & Policy, a firm that advises on public health policy. In the past, he has worked in an advisory capacity for Alpharma Inc. on issues of a public health nature.

Bio: Mr. Barnes is responsible for strategic growth, business development, and client satisfaction for DCBA Law & Policy and its Center for Lawful Access and Drug Deterrence (CLAAD). Prior to establishing DCBA in 2004, Mr. Barnes served as confidential counsel in the Office of National Drug Control Policy, where he provided direction.
on policy and program matters aimed at reducing the demand for illicit drugs. Leading up to his presidential appointment, Mr. Barnes worked for The Perls Law Firm.

Mr. Barnes obtained his Juris Doctor degree from George Mason University School of Law. He earned a master’s degree in international economic policy from La Universidad de Belgrano in Buenos Aires, Argentina, where he lived and studied as a Rotary Foundation International Ambassadorial Scholar. He received his bachelor’s degree summa cum laude from Flagler College.

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52. In 2001, in rejecting a petition for the rescheduling of marijuana, the FDA stressed:

The agency cannot conclude that marijuana has an acceptable level of safety without assurance of a consistent and predictable potency and without proof that the substance is free of contamination. If marijuana is to be investigated more widely for medical use, information and data regarding the chemistry, manufacturing and specifications of marijuana must be developed.

55. As technologies advanced, synthetic medicines appeared, necessitating the promulgation of a subsequent treaty, the Psychotropic Convention of 1971.
56. Cannabis was generally not smoked at that time for medical purposes.
57. “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.” McCarberg, WH and Barkin RL, “The Future of Cannabinoids as Analgesic Agents: A Pharmacologic, Pharmacokinetic, and Pharmacodynamic Overview,” (2007) American Journal of Therapeutics 14(5): 475-483, 476 (emphasis added).
62. FDA, Guidance for Industry: Botanical Drug Products, 2004, http://www.fda.gov/cder/guidance/4592f1.pdf (hereinafter Botanical Guidance) at p. 34, (“A botanical product submitted for marketing approval as a drug will be treated like any other new drug under development... [P]revious human experience may be insufficient to demonstrate the safety of a botanical product, especially when it is indicated for chronic therapy.”)
63. This is the last stage of human research before the submission of a marketing application or NDA.
66. GW Pharmaceuticals, Research & Development / Cannabis Cultivation. [Website: http://www.gwpharm.com/research_cultivation.asp]


67. Such efforts are not confined to the U.S.; see, e.g., Echo Pharmaceuticals (the Netherlands) (Namisol, a naturally-derived THC in sublingual tablet form). The U.S. (through NDA) has also provided research-grade cannabis to a number of researchers whose studies have been funded by grants from the Center of Medicinal Cannabis Research, which is based at the University of California San Diego. The results of a number of these studies have been published (www.cmcr.ucsd.edu/geninfo/marijuana.htm) and respond to the IOM's statements that such clinical trials serve "as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems." Marijuana and Medicine, supra, at p. 11.

68. Indeed, even the staunchest herbal cannabis advocates are recognizing the need to develop standardized cannabis pharmaceutical products with "innovative formulations." [Website: http://www.phyla.com]

69. The path of Cannasat is instructive. Cannasat, the only firm in Canada devoted to the development of cannabinoid medications, initially extolled the benefits of herbal cannabis plant material. Recently, it sold off its ownership interests in the cannabis cultivation program operated under contract from Health Canada and is developing synthetic cannabinoids with "proprietary formulations and drug delivery technologies." [Website: http://www.cannasat.com/news-5.html http://www.cannasat.com]

70. The Institute of Medicine has described the many financial and other challenges that would be faced by a developer of legitimate cannabis-derived pharmaceutical products, even if a parallel, "informal" system of dispensaries did not exist. To allow such dispensaries would increase these disincentives and potentially prevent the U.S. from responding to the IOM's call for the development of rapid-onset, alternative delivery systems for cannabinoids- or cannabinoid-based products. Marijuana and Medicine, supra, at pp. 193-219.

71. For example, the Elixir Sulfanilamide disaster led to the enactment of the 1938 Food, Drug & Cosmetic Act (FDCA), June 25, 1938, c.675, 52 Stat. 1040, which required, among other things, that new drugs be tested for safety before marketing. The thalidomide tragedy in Europe led to the passage of the Drug Amendments of 1962, Pub. L. 87-781, sec. 1, Oct. 10, 1962, 76 Stat. 780 (also known as the Kefauver-Harris Amendments), which required that products be proved to be both safe and effective before marketing.


74. Dietary supplements are already subject to a lower standard of regulatory scrutiny because they are presumed to be less dangerous than prescription medications and because they are not intended to be used in diagnosing, mitigating, treating, or curing disease. See, the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 U.S.C. §321(ff). Dietary supplements are orally ingested. FDA Botanical Guidance at p. 3.

75. See The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. 103-417. [Website: http://www.fda.gov/opacom/laws/DSHEA.html] Whether a product is a drug under the FDCA turns on its "intended use." "Intended use," in turn, is created by claims made by or on behalf of a manufacturer or distributor of the item to prospective purchasers, such as in advertising, labeling, or oral statements. 21 U.S.C. §321(g)(1)(B); Botanical Guidance at p. 2. Dietary supplement manufacturers, distributors, or retailers cannot make specific health claims. See, e.g., U.S. v. 24 Bottles "Starling Vinegar and Honey Aged in Wood Cider Blended With Finest Honey Contents 1 Pint Product of Sterling Cider Col., Inc., Sterling, Mass.," 338 F.2d 157 (2nd Cir. 1964); Kordel v. U.S., 335 U.S. 345 (1948).

76. See, e.g., "California Law Enforcement Investigating 'Pot Docs'" (July 8, 2008), [Website: http://www.officer.com/web/online/Top-News-Stories/California-Law-Enforcement-Investigating-Pot-Docs/1S31450]

77. Gonzales v. Raich, 545 U.S. 1 (2005).


79. If physicians prescribe unapproved medications (those that are not approved by the state or federal regulatory agency), and a patient suffers harm as a result, the physician's professional liability policy may not cover a claim for damages. See, Educating Voices "The Potential Medical Liability for Physicians Recommending Marijuana as a Medicine," (white paper). [Website: http://www.educatingvoices.org/EVI_WhitePaper1.pdf]


82. Bone, M, MD, "Laetrile Drug Never Proved to be Effective Cancer Treatment," The Palm Beach Post (Mar. 20,


66. For example, Salvia divinorum (whose active constituent is salvinorin A) is a herb that is increasingly used by the public for its hallucinogenic effects. Salvia is not currently controlled under the CSA, although the DEA is observing it closely. As of November 2008, thirteen states had enacted legislation placing regulatory controls on Salvia divinorum and/or salvinorin A; a number of those states placed the substances in schedule I of state law. Proposed legislation is pending in a number of other states. DEA, "Drugs and Chemicals of Concern," Nov. 2008. http://www.deadiversion.usdoj.gov/drugs_concern/index.html.


68. DEA, State Prescription Drug Monitoring Programs. http://www.deadiversion.usdoj.gov/safeny_monitor.htm. When controlled substances are at issue, the federal government also has authority to regulate directly some aspects of a physician's medical practice. Under the CSA, physicians who prescribe or dispense controlled substances must hold a registration from the DEA, and such controlled substances must be prescribed for a legitimate medical purpose and in the course of regular professional practice. 21 C.F.R. §1306.04(a); U.S. v. Moore, 423 U.S. 122, 137, 140-42 (1975). Although states bear the primary responsibility for preventing and punishing the diversion of (prescription) controlled drugs by health care providers, the DEA in egregious cases may investigate and revoke the registration of (and even criminally prosecute) a physician or other health care provider who facilitates and/or promotes drug abuse and addiction.

69. See, e.g., "California Law Enforcement Investigating 'Pot Docs'" (July 8, 2008). http://www.officer.com/web/online/Too-News-Stories/California-Law-Enforcement-Investigating-Pot-Docs/1531450. The Medical Board of California has promulgated guidelines for physicians who recommend cannabis; however, there has been very limited enforcement. http://www.medbrd.ca.gov/Medical_Marijuana.html Physicians who recommend cannabis can avoid the need for a DEA registration if they do not prescribe other controlled substances.

70. Salmonella and E. coli are common bacterial contaminants that can be transmitted to botanical material through improper handling techniques.

91. San Francisco regulations state that dispensary operators must require employees only to "wash hands" and "use sanitary utensils" when handling cannabis, rather than use sterile gloves and instruments. Sec. 3312(b)(3).

92. As one dispensary advertises: "We are also experienced and knowledgeable about the various medications and how they work for various ailments, so we can steer you toward an answer, not just another dead end." http://greenendragoncoco.com/default.htm?gclid=CKWtrq6jSxkCFRebapodxhFTZg http://www.mlive.com/news/flint/index.ssf/2009/03/group_to_offer_marijuana_advc.html http://www.sanfranciscocannabisclubs.com/directory/san-francisco-green-door.htm (patients can expect to deal with "knowledgeable" staff members).


94. Many cities have no regulations and, indeed, have issued bans or moratoria. http://www.scribd.com/doc/294569/Medical-Marijuana-moratorium-map.


96. Cannabis is a highly abuseable substance and, if determined to have an accepted medical use in treatment in the U.S., would remain subject to the closed system of distribution required by the CSA. State regulation does not fulfill this requirement.

97. Manhattan Project, supra.

98. Of course, this "laboratory" is a far cry from currently-acceptable scientific standards ("looks like a bachelor pad with a locked room in the back"). Id.

99. Id.

100. For example, bills are pending in Illinois, Minnesota, New Hampshire, and New York, among others to decriminalize cannabis for medical use. http://www.mpp.org/legislation.

101. For example, a bill is currently pending in the Rhode Island legislature to amend the existing "medical
marijuana" law to authorize cannabis dispensaries. This bill has gained more force following Attorney General Eric Holder’s remarks, although it failed in the state House of Representatives last year. Members of the House have stated that the Attorney General’s comments have caused them to view the proposal “much more favorably” than last year. Needham, C., “Bill Would License Dispensaries to Sell Medical Marijuana” (Mar. 5, 2009). http://www.projo.com/news/content/MARIJUANA_BILL_03-05-09_UNDOHRGIN_v17.37884c1.html


103. Single Convention, preamble, Art. 4c.

104. The need for the practice of medicine to be “evidence-based” has become well-established, particularly in the Western world. For several decades, scientists had been conducting randomized, placebo-controlled clinical trials to investigate the safety and efficacy of investigational medical products. Chow, S. and Liu, J., “Design and Analysis of Clinical Trials,” p. 4 (1998). Then, as now, the results of such clinical trials formed the basis both of governmental regulators’ marketing approvals and physicians’ prescribing practices. See Guyatt, G. et al., “Evidence Based Medicine: Principles for Applying the Users’ Guides to Patient Care,” 284 Journal of the American Medical Association 1290 (Sept. 13, 2000).

105. Cannabis and cannabis resin were placed in Schedule IV, the treaty’s most restrictive schedule, whereas oral cannabis preparations, i.e., tinctures and extracts, were placed in Schedule I, along with most other narcotic drugs. The Single Convention’s schedule structure does not parallel that of the Controlled Substances Act, in which Schedule I is the most restrictive.


109. The treaty imposes other, very specific restrictions on the cultivation of cannabis, opium, and coca. Article 22 requires a Party to prohibit cultivation, if the Party concludes in good faith that the “prevailing conditions” in the country make such prohibition the most suitable measure of protecting the public health and safety. Furthermore, a Party that prohibits such cultivation must “take appropriate measures” to seize and destroy any plants that are illegally cultivated, except for small quantities that the Party itself may need for scientific or research purposes.

110. The Commentary also indicates that, under the Single Convention, all licensed cultivators “should to the greatest extent possible, be located in the same part of the country, and be contiguous, in order to facilitate more effective control.” Commentary at p. 280. This provision would not permit the establishment of cannabis cultivation sites in numerous locations all over the U.S.

111. Preparations of cannabis, such as pharmaceutical-grade extracts and tinctures, are exempt from the government monopoly on wholesale distribution. Single Convention, art. 23, para. 1(e). The treaty also does not extend the government’s exclusive rights to “medicinal opium and opium preparations.” Id. at art. 23, para. 2(e). “Medicinal opium” is a form of opium powder to which lactose has been added to reduce the morphine content to the standard of about 10 percent.” Commentary at p. 21-22. In other words, the term “referred to a product which had not only been extracted from the opium poppy but had also undergone several further processes … to prepare it for use in other drugs and to obtain a specific and standardized content of morphine, its primary active ingredient.” DEA, “Lyle E. Craker; Denial of Application,” 74 Fed. Reg. 2101, 2104 (Jan. 14, 2009) at p. 2116. “[T]here were recognized standards for the substance’s manufacture and composition and … the drug had an accepted medical use in humans.” Id. By contrast, “there are no recognized standards with respect to herbal marijuana.” Id. Therefore, cannabis, even if intended for medical use, d
From Mockery to Medicine: The Story of the Development of a Serious Modern Medicine

Andrea G. Barthwell, MD, FASAM

Introduction

In the United States, the effort to legalize cannabis for use as "medical marijuana" has focused on making it available to people as a home remedy, or perhaps an herbal treatment akin to a dietary supplement, but not as a Food and Drug Administration (FDA) - approved medicine. To obtain such approval, a therapeutic product must be quality-controlled in all aspects of manufacture, standardized by composition and dose, tested in preclinical and clinical studies, and administered by means of an appropriate delivery system or dosage form. It must, in short, meet the rigorous standards for quality, safety and efficacy that have been laid down by regulatory authorities. 

Crude herbal cannabis could never pass the FDA's rigorous standards.

The FDA recognizes that under appropriately controlled conditions, modern research and technologies enable complex botanical materials to be developed into pharmaceuticals in accordance with both scientific and regulatory rigor. The agency has issued a guidance document for these circumstances, acknowledging that complex composition is not inherently problematic. Rather, as with all pharmaceutical products, the important factors are the application of quality control processes at each stage in the manufacturing process; characterization, specification, and standardization of the components; and the completion of appropriate preclinical and clinical studies—in other words; proof of quality, safety, and efficacy.

Crude herbal cannabis varies significantly in composition and consistency, depending on which strain is being propagated and under what conditions it is cultivated, harvested, stored, and prepared. Persons using crude herbal cannabis use materials that vary in quality and content. These materials may be contaminated with harmful pesticides, fungi, or heavy metals. Such contaminants have the potential to pose a threat to both seriously ill and healthy people. There is at least one report of death from a rare neurological condition, which may have occurred as a complication of an allergic reaction to pesticide-laden cannabis handled at the dispensary.

Evidence-Based Medicine

Crude cannabis and the methods used to deliver it to patients have not met the minimum standards required of legitimate medicines and, therefore, do not belong in our system of modern medical practice. Modern medical practice is evidence-based. In advising patients, physicians rely in large part upon the results of controlled clinical trials conducted in accordance with established scientific principles. Preclinical studies and early (Phase 1) clinical trials demonstrate whether the product is likely to be harmful to humans. Randomized, double blind, placebo-controlled clinical trials (Phases 2 and 3 clinical trials)—the "gold standard" of scientific research—provide information about a medical product's safety and efficacy that usually accurately predicts real world expectations for a new medication.

GW Pharmaceuticals' Development Program

GW Pharmaceuticals (GW) has embarked on a full pharmaceutical development program for cannabinoids that pursues both scientific and regulatory rigor, making it the first company in the world to produce a complex, heterogeneous pharmaceutical product derived from the cannabis plant. As GW's research has shown, the process of developing botanically derived cannabinoid medicines is a challenging one, necessitating standardized raw materials and innovative extraction methods for the non-water soluble active ingredients.

Moreover, GW has rigorously adhered to the high principles of science and evidence-based medicine in its development program, having already conducted eight Phase 3 clinical trials and numerous smaller Phase 1 and Phase 2 studies with more than 2,000 patients participating. These clinical studies have investigated the use of Sativex® in the treatment of symptoms of multiple sclerosis, including spasticity, bladder dysfunction, tremor, spasm, sleep disturbance, pain, neuropathic pain of various origins—such as spinal cord injury, diabetic neuropathy, MS, brachial plexus avulsion, rheumatoid arthritis, and cancer pain.

Using the latest technology, GW produces highly standardized cannabis "chemovars"—plant strains characterized by their chemical composition—that serve as the starting materials for its pharmaceutical development process. Computer-controlled glasshouses rigorously monitor and control growing conditions. Sensors automatically adjust light exposure to respond to changes in length and quality of daylight. Organic growing medium and specific quality control techniques ensure that no pesticides, heavy metals or microbiological contaminants are present. Botanists employ sophisticated breeding techniques to create unique chemovars that express specific cannabinoid ratios. Clonal reproduction maintains cannabinoid ratios and chemical composition throughout subsequent generations.

GW cultivates two primary cloned lines not normally found in nature, one in which cannabidiol (CBD), a non-psychoactive cannabinoid, is predominant. CBD is believed to significantly attenuate delta-9-THC effects.
9-tetrahydrocannabinol (Delta-9-THC) - associated side effects, such as intoxication and tachycardia 15(6). This CBD clonal line and a predominantly Delta-9-THC plant strain were developed through applied Mendelian genetics and are proprietary to GW.

Manufacture and Formulation Considerations
Cannabinoids are not water-soluble; therefore, studies are required to identify excipients that will permit the formulation of cannabinoids into finished pharmaceutical products. Cannabinoids, particularly Delta-9-THC, are also very unstable; therefore, research is required again to select formulations and to structure the manufacturing and storage processes to ensure that the medicines will maintain an appropriate shelf life. A small change in formulation can have substantial effects on both bioavailability and stability. GW has conducted numerous trials to ascertain the optimal formulation for its lead product, Sativex®, which contains a specific proportion of cannabinoids with ethanol and propylene glycol excipients.

Once crude cannabis plant material is standardized, as is achieved in the manufacture of Sativex®, it is only the first step in producing a modern medicine. A cannabis-based medicine must be fully researched and strictly regulated at every step in its manufacturing cycle; therefore, the subsequent steps of the manufacturing process—from harvesting to drying to the various steps of extraction and formulation—are also standardized and subject to stringent quality control testing procedures. GW blends the extracts from the two clonal lines to produce Sativex®, a ratio of 1.08:1 of Delta-9-THC and CBD. The final product is highly characterized, and tight specifications are set for all the significant cannabinoids and other components, such as terpenes, plant waxes, and flavonoids. These are common plant components present in many food and flavoring items.

Delivery System Considerations
Once standardized in composition, a cannabinoid medication must be administered in a manner that enables a patient to obtain a reliable dose with predictable effect. It is especially important to allow the patient to adjust his or her dose in order to obtain relief of symptoms while minimizing side effects, particularly disabling psychoactivity. It is also essential that the delivery system does not expose the user to harmful impurities, such as pyrolytic products.

There is no proven safe and reliable delivery system for crude herbal cannabis. If crude cannabis is smoked, it exposes seriously ill patients to dangerous pyrolytic products. If it is eaten in baked goods, ground and packaged in gel caps, or consumed as tea, the intestinal absorption is very erratic from day to day or even throughout one day, and hence its effect, including its psychoactive effect, is quite variable and unpredictable. It is also subject to first-pass metabolism to metabolites with more psychoactivity than the parent compound. In such delivery methods the dose and composition are uncertain.

Pulmonary Delivery Carries Associated Risks and Harms
Tests of the crude cannabis plant in all studies to date show that burn-and-inhale administration is simply a toxic alternative delivery system for high doses of Delta-9-THC. Given that oral Delta-9-THC is available as a Schedule 3 prescription drug, one might argue that there should be no need for smoked crude marijuana. The individuals who prefer the smoked, home remedy approach say they do so because smoking marijuana gives them the ability to titrate their dose or control rate of onset of action. The formulation issue is a valid one in clinical medicine that needs to be addressed and has been done so by GW such that patients can achieve a therapeutic effect with significantly reduced risk of psychoactive effects.

Vaporization, a popular trend among cannabis smokers, does not resolve these issues. A recent study showed that when herbal cannabis is vaporized, several harmful carcinogens (polyaromatic hydrocarbons)—while reduced—were still delivered to the lungs 16. Furthermore, currently available vaporizers do not provide the precise standardization of dose necessary for a prescription medicine. In addition, when patients inhale cannabis (whether smoked or vaporized), their Delta-9-THC blood levels rise rapidly to high levels, making it probable that many of them will not be able to control psychoactive side effects. Rapid increases in Delta-9-THC blood levels are also associated with greater tendency to intoxication and dependence.

Unique Delivery System Developed
Because Delta-9-THC is psychoactive, it is essential that a Delta-9-THC-containing product be delivered in a manner that enables a patient to remain within the "therapeutic window," i.e., predictably to obtain symptom relief without experiencing untoward central nervous system side effects. Seriously ill patients with debilitating chronic disorders do not wish to "trade one disability for another" to be intoxicated; they want to work, care for their families, and be productive. Accordingly, the delivery system must not only provide standardized doses but must also enable the physician and patient to manage the dosing increments. The regulated system of medicine offers the only hope in the area of formulation to safely address the delivery system needs of patients.

To address this issue, GW Pharmaceuticals pioneered the development of an oromucosal spray for the delivery of Sativex®. Its onset of action is 15-40 minutes, which is rapid enough to enable chronically ill patients to titrate their dose, but not so rapid as to be rewarding for its euphoriant effects. The oromucosal spray contains exactly 100 micro liters of Sativex® (2.7 mg. of Delta-9-THC and 2.5 mg. of CBD) 17. GW has monitored "intoxication scores" of its patients, and the level of intoxication among patients (who are receiving relief of symptoms) is essentially no higher than placebo 9. It is, therefore, clearly not the case that patients achieve symptom relief only at the cost of intoxication. Furthermore, many patients have been taking Sativex® for one to four years and have not escalated their dose during that time 9 18. Although evidence suggests that illicit users may become tolerant to the psychoactive effects of cannabis and must increase their use, patients using Sativex® do not develop tolerance to
its therapeutic benefits.

Additionally, a group of MS patients on Sativex® for one year or more voluntarily stopped Sativex® administration abruptly. While symptom re-emergence occurred within seven to 10 days for most, none had significant withdrawal symptoms 16, and all who resumed the medicine regained symptomatic control at previously established doses. It is common to see symptom re-emergence after adequate control when medications are abruptly discontinued, sometimes paired with withdrawal.

This intermediate-onset delivery system, which also permits patients to take small increments of medicine, is believed to be an improvement over other forms of administration, particularly oral administration. Gastrointestinal absorption of oral Delta-9-THC exposes the compound to a first pass effect and hepatic metabolism of Delta-9-THC to 11-hydroxy-THC, thought to be more psychoactive than Delta-9-THC with an onset of effect that is long and unpredictable. Patients, therefore, cannot reliably titrate their dose after oral administration to avoid side effects, including psychoactivity. As the Institute of Medicine has stated 17.

The poor solubility of Marinol® in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10-20% of an oral dose reaches the systemic circulation. The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing...
Variation in individual response is highest for oral Delta-9-THC and bioavailability is lowest.

Abuse Liability Varies with Rate of Change of Blood Level Over Time
Inhaled Delta-9-THC is neither an optimal nor desirable delivery system for most patients. When Delta-9-THC is inhaled (as in smoking or vaporizing cannabis), Delta-9-THC blood levels rise to high levels quickly, with the resulting rise in blood level over a short period of time associated with greater tendency to intoxication and dependence. In a Phase I study, using a predominantly-Delta-9-THC extract delivered by means of a high technology vaporizer, GW found that concomitantly high intoxication levels accompanied such a rapid Delta-9-THC blood level rise 17. A similarly high rise in Delta-9-THC blood levels was demonstrated in a recent Phase I trial that tested an inhaled version of dronabinol; therefore, it is likely that many patients who inhale Delta-9-THC will have a difficult time controlling intoxication and remaining within the therapeutic window 20. Most patients with chronic conditions do not need an immediate onset product, particularly when there is such an undesirable tradeoff of symptom relief vs. intoxication. Sativex® onset of action of 15-40 minutes provides sufficiently rapid symptom relief for such conditions, especially as patients learn over time to adjust their small doses to stabilize and maintain therapeutic blood levels.

The Scheduling of Cannabinoid-Containing Products under the Controlled Substances Act
Under the federal Controlled Substances Act (CSA), both cannabis and Delta-9-THC are Schedule I substances. If a cannabis-derived product like Sativex® were successful in obtaining FDA marketing approval, that specific product would need to be transferred out of Schedule I to another schedule, since FDA approval demonstrates that the product has “an accepted medical use in the US.” This would not, however, necessitate a rescheduling of either herbal cannabis or Delta-9-THC. For example, Marinol® is located in Schedule III, while Delta-9-THC remains in Schedule I. Moreover, even if cannabis and Delta-9-THC (as active ingredients) were moved to Schedule II, that would not mean that crude herbal cannabis, or any cannabis or Delta-9-THC preparation, would become immediately available to patients by prescription. Rather, each and every medical product in interstate commerce must have gone through the FDA process on its own merits and must have satisfied FDA’s intense scrutiny before physicians may prescribe and pharmacists may dispense it. Opium and coca leaves are in Schedule II, but crude opium or coca products are not distributed to patients. The entire “rescheduling of cannabis” argument made by cannabis advocates demonstrates a profound misunderstanding of the process by which serious prescription medicines become available to patients in the US.

Conclusion
Sativex® is a pharmaceutical product standardized in composition, formulation, and dose, which is administered by means of an appropriate delivery system, and which has been—and continues to be—tested in properly controlled preclinical and clinical studies. It is not crude cannabis, which is none of those things. Acceptance of Sativex® [and its proof of efficacy] for specific indications does not suggest the acceptance of crude cannabis or prove its medical usefulness for the reasons set forth and many others. All medicinal products must be subjected to, and satisfy, the FDA’s rigorous scrutiny before becoming available to patients in need. GW has consistently maintained that crude herbal cannabis can never meet the regulatory standards of the FDA and those of regulatory bodies in most other countries around the world 21. These standards are mandatory if the modern medical model—informing patients working with and being advised by knowledgeable physicians to identify appropriate treatment options—is ever to be attined with a cannabis-based medicine.

It is not surprising that the concept of “medical marijuana” has been foisted on a largely unwilling and disapproving medical profession by legislative and ballot initiatives. Physicians who want medicines to meet the tests of quality, safety, and efficacy are not its proponents. Rather, the primary supporters are those whose ultimate agenda is to legalize marijuana for non-medical purposes. For the safety of patients and the security of physicians, physicians must draw a bright line between approved, legitimate medications and drugs of abuse that are used for the purpose of obtaining a euphoric “high.” Physicians must insist that the medicinal products they recommend to patients be subjected to, and satisfy, the FDA’s rigorous scrutiny.


6. Collin C. A cannabis-based medicine (Sativex) has sustained efficacy in the treatment of spasticity in multiple sclerosis. Association of British Neurologists; 2005 April 1; Belfast, Northern Ireland; 2005.


18. Canada has approved Sativex® for the treatment of neuropathic pain in multiple sclerosis. GW is currently preparing additional European regulatory submissions for other medical indications. The UK has authorized Sativex® to be prescribed on a named patient basis to patients whose physicians believe they may benefit from the product. Additionally, the Catalan government in Spain has permitted it to be prescribed on a compassionate basis. On January 3, 2005, GW announced that the FDA had agreed to permit Sativex® to proceed to Phase III clinical trials, the final stage of research that a product must undergo before it is submitted for marketing approval. GW will test Sativex® in patients with advanced cancer, whose pain is not being adequately controlled with opiates. The trials will commence in the later part of 2005 and a marketing application should be submitted 24-36 months after the trials begin. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Multiple Sclerosis. 2006;(in press).


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I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled except for the following:

Consultant, GW Pharmaceuticals

Author: Andrea G. Barthwell, MD
Date: July 17, 2006