



## **The Scope of Federal Control Over Controlled Substances and the Prescription Drug Approval Process**

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### **The Food, Drug, and Cosmetic Act Provides the Primary Source of Control over the Production and Marketing of Medications.**

The United States has developed one of the most stringent pharmaceutical regulatory systems in the world. That system governs all aspects of the pharmaceutical development process, including products containing controlled substances. The Food, Drug, and Cosmetic Act (FDCA) establishes exacting scientific criteria and standards that must be met before medications may be made available to patients. This process is designed to ensure that patients receive medications that are safe and efficacious for their intended use. Since the beginning of the 20<sup>th</sup> century, the federal government has had the primary responsibility for the regulation of products intended for medical use, particularly those containing controlled substances.

This federal regulatory system was developed in response to serious threats to patient health and safety. In 1900, medical products were essentially unregulated. Many “patent” medicines contained significant amounts of opium, cocaine, alcohol, and cannabis. “Accidental” addiction became a serious problem. See Whitebread, C., “The History of the Non-Medical Use of Drugs in the United States,” (speech to the California Judges Association 1995). When the States failed adequately to address the problem, Congress acted by passing the Food and Drug Act, Act June 30, 1906, c.3915, 34 Stat.768, which required, among other things, that medications indicate on the label the quantity of alcohol, morphine, opium, cocaine, heroin, or cannabis that they contained.

Over the following decades, federal legislation was gradually expanded to address various abusive practices or events involving significant suffering and harm. For example, the Elixir Sulfanilamide disaster led to the enactment of the 1938 Food, Drug & Cosmetic Act (FDCA), Act 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.

Around the world, the FDCA’s criteria have become the “gold standard” for the quality, safety, and efficacy of medical products. Virtually all states refer to, and rely upon, the FDA’s assessment of a

product's risk/benefit profile and suitability for marketing.<sup>1</sup> By contrast, a State may wish to maintain greater or additional restrictions on pharmaceutical products than those imposed under federal law, i.e., by permitting injured patients to bring fraud, failure to warn and/or product liability actions against manufacturers of FDA-approved products, largely based on alleged deficiencies in the product's labeling.<sup>2</sup> This is particularly true with regard to products containing controlled substances.<sup>3</sup> However, such state laws (both common law and legislation) are meant to enhance, not undermine, FDA's substantive determinations of safety and efficacy, by extending a right of compensation to injured patients.

The FDA also assesses the nature and quality of the processes used to manufacture a medication, and assures that the medication is both free of contamination and consistent in content from batch to batch. Products must be properly labeled with instructions for use.<sup>4</sup> Promotional claims must be limited to the approved medical indication and all advertising (including direct to consumer) must be properly balanced with information on risks/adverse events. Physicians may prescribe, pharmacists may dispense<sup>5</sup>, and patients may purchase, only those products that have passed through the FDA approval process.

The supremacy of FDA regulation is further evidenced by the fact that the FDCA, its implementing regulations, FDA guidance documents, and other federal laws generally govern the conduct of clinical trials. Most states do not impose their own state-specific requirements for clinical trials. Clinical trials undertaken in a state therefore must be conducted and designed in a manner consistent with federal requirements, particularly those regarding the treatment of human subjects. Serio JC, Tichner JB, and Dilley ME, *State-by-State Clinical Trial Requirements Reference Guide* (Parexcel 2004).

It is true that, for the most part, the "practice of medicine," i.e., a physician's method of diagnosis, assessment, documentation, monitoring, and follow-up, has traditionally fallen within the purview of state regulation. The FDA has frequently commented that the FDCA does not regulate the practice of medicine; for example, a physician may lawfully prescribe "off-label" a product that is FDA-approved for a particular indication. State licensing boards determine whether or not such practices fall within acceptable professional standards. 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.<sup>6</sup> Health care facilities are

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<sup>1</sup> There are limited examples of state laws that are intended to parallel the FDCA in cases involving those few products that were manufactured, distributed, and sold only within a single state. See, e.g., California's enactment of the Sherman Food, Drug, & Cosmetic Law ("Sherman Law"), Calif. Health & Safety Code sec. 109875 *et seq.* The Sherman Law requires that, in order to be approved as a medical product, a "new drug" must meet exacting scientific standards parallel to those established under the FDCA. However, as a practical matter, very few pharmaceutical products are approved pursuant to such state laws.

<sup>2</sup> *Wyeth v. Levine*, 129 S.Ct. 1187 (Mar. 4, 2009). There are currently many federal multidistrict actions in which plaintiffs challenge the adequacy or truthfulness of FDA-approved drug labeling. State courts are also inundated with similar mass-tort suits. Brief for the Pharmaceutical Research and Manufacturers of America as Amicus Curiae Supporting Petitioner at p.8.

<sup>3</sup> For example, while the branded product Marinol, which contains synthetic tetrahydrocannabinol (THC), was rescheduled in 1999 to Schedule III of the CSA, see 64 Fed. Reg. 35928 (July 2, 1999), it was not rescheduled under California law until 2000 and in other states even later.

<sup>4</sup> Current "medical marijuana" distribution models provide virtually no control over dose, with the dosage established entirely by the individual patient. This is not the accepted standard for other controlled substances and may encourage excessive and inappropriate use.

<sup>5</sup> Pharmacists are permitted to compound medications only under very limited circumstances not involving large numbers of patients. FDA, Warning Letter: Hal's Compounding Pharmacy, Inc. (04-Dec-06) <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076195.htm> (emphasis added). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124736.pdf> . FDA, Compliance Policy Guide, sec. 460.200 ("Pharmacy Compounding"), 67 Fed. Reg. 39, 409 (June 7, 2002).

<sup>6</sup> 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

monitored and licensed by state departments of health services. 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

However, even in this area, federal regulation is common, particularly when controlled substances are prescribed. For example, under the Controlled Substances Act (CSA), a physician must obtain a registration (license) from the Drug Enforcement Administration (DEA) in order to prescribe or dispense a controlled substance for medical use; pharmacies must also be registered. Under the CSA, controlled substances must be prescribed by an individual practitioner 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). The DEA may seek to suspend or revoke a physician's/pharmacy's registration if the registrant commits certain acts, including acts "inconsistent with the public interest." 21 U.S.C. sec. 823(a)(4). Furthermore, in order to dispense narcotics to addicted patients for purposes of maintenance or detoxification, a physician must be specially registered by the DEA as an opiate treatment program (OTP). See 21 U.S.C. sec. 823(g). In addition, under the recent Drug Abuse Treatment Act, 21 U.S.C. sec. 823(g), qualified physicians may, without obtaining an OTP registration and subject to a number of requirements, prescribe narcotic products in Schedules III-V, if such products have been approved by the FDA for treatment of addiction.<sup>7</sup> See 21 U.S.C. sec. 823(g)(2). Finally, while the First Amendment protects a physician's right to provide a patient with medical information and advice about any potential medical treatment, a physician can be subject to federal sanctions if he/she provides such advice deliberately to enable the patient to obtain an illegal substance, such as cannabis. See *Conant v. Walters*, 309 F.3d 629 (9<sup>th</sup> Cir. 2002). Hence, in many respects, the federal government has significant authority directly to affect the practice of medicine.

In short, federal law governs the entire spectrum of steps by which all new medications are researched, manufactured, and made available by prescription to patients.

### **Federal Law Determines Which Controlled Substances May be Made Available for Medical Use**

Federal law sets forth conditions under which controlled substances may be lawfully prescribed solely for medical purposes. The CSA is the primary statutory tool by which such determinations are made.<sup>8</sup>

The CSA establishes a comprehensive scheme that 1) provides a mechanism (the scheduling process) by which the results of scientific research may be used to ensure that patients will have access to medications containing controlled substances; and 2) prohibits the possession, sale, etc. of controlled substances or products for nonmedical use.

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Voices "The Potential Medical Liability for Physicians Recommending Marijuana as a Medicine," (white paper). [http://www.educatingvoices.org/EVI\\_WhitePaper1.pdf](http://www.educatingvoices.org/EVI_WhitePaper1.pdf).

<sup>7</sup> Many physicians early in the 1900s felt obligated, as a part of their medical practice, to prescribe controlled substances to those unfortunate individuals who had become addicted to opiates in the years before the original FDCA was enacted. Congress rejected the concept that such prescribing constituted the legitimate practice of medicine and, in 1914, enacted the Harrison Narcotics Act, 38 Stat. 785, Comp. St. sec 6287g-6287q (1914), *as amended* 26 U.S.C. 4701-36. The Harrison Act, although ostensibly a revenue measure founded on the Taxing Power, essentially precluded the prescription of opiates to addicts for maintenance purposes. In 1937, the Marihuana Tax Act, 26 U.S.C. sec. 4741-76, created strong disincentives for physicians prescribing cannabis, thereby effectively making it unavailable for medical use. These acts were replaced by the CSA.

<sup>8</sup> Such determinations and distinctions may also be made directly by Congress. See, e.g., the Hillary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law [PL] 106-172). This law created a differentiated scheduling scheme, directing the Attorney General/DEA to amend the CSA by listing GHB (a "date rape" drug) as a Schedule I agent and creating an exception to place FDA-approved formulations of GHB in Schedule III.

An integral part of this scheme is the scheduling process. The CSA places controlled substances in one of five schedules, depending on the substance's recognized therapeutic usefulness, safety for use under medical supervision, and abuse liability. 21 U.S.C. sec. 812.<sup>9</sup> Cannabis/marijuana, ibogaine, mescaline, and peyote are botanical hallucinogens listed in Schedule I. Schedule I substances are those determined to have:

- A high potential for abuse;
- No currently accepted medical use in treatment in the US<sup>10</sup>; and
- A lack of accepted safety for use under medical supervision<sup>11</sup>.

Substances in Schedule II have:

- A high potential for abuse;
- A currently accepted use in treatment in the US or a currently accepted medical use with severe restrictions; and
- Abuse of the substance may lead to severe psychological or physiological dependence.<sup>12</sup>

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

Schedule I and II substances are, for the most part, subject to the same restrictions and requirements under the CSA, including manufacturing and procurement quotas, security measures, recordkeeping, import/export permits, etc. However, substances in Schedule I may only be used in research studies by investigators who 1) have protocols that have been approved by the FDA and 2) have received research registrations from the DEA. Outside of this system, all possession, cultivation, distribution, etc., of a Schedule I substance, such as cannabis, is illegal under federal law, even if decriminalized under state law.

The standards and criteria of the CSA are coordinated with those of the FDCA to determine the circumstances under which a controlled substance with abuse potential may, when properly formulated,

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<sup>9</sup> The following factors, often referred to as the "eight factor analysis," determine the schedule to which a substance is assigned:

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

21 U.S.C. sec. 811.

<sup>10</sup> In a proceeding which seeks to move a drug from Schedule I to Schedule II, the DEA will examine the following factors in determining whether the drug has a "currently accepted medical use":

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

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

<sup>11</sup> 21 USC sec. 812(c) (Schedule I (c)).

<sup>12</sup> 21 USC sec. 812(c) (Schedule II (a)). Substances in Schedules III-V have decreasing levels of abuse potential and are subject to lesser degrees of control.

tested, and delivered as a pharmaceutical product, be made available as a prescription medicine.<sup>13</sup> Before making the required statutory findings relating to a product's proposed schedule, the Attorney General (delegated to the DEA) must receive, from the Secretary of Health and Human Services (delegated to FDA), a medical and scientific evaluation of, and recommendations upon, certain criteria relating to scientific knowledge, pharmacological effect, and abuse potential of the drug or other substance in question. These recommendations are binding on the Attorney General as to scientific and medical matters.<sup>14</sup> FDA approval constitutes "accepted medical use," and is sufficient to remove a product from Schedule I.<sup>15</sup> The FDA, under the recent Food and Drug Administration Amendments Act of 2007 (FDAAA), also has authority to require a manufacturer to develop a Risk Mitigation and Evaluation Strategy (REMS) to ensure that the benefits of a product outweigh its risks, including, among other things, risks of abuse and overdose. 21 U.S.C. sec. 355-1.

In addition to, and integrated with, the scheduling provisions, the CSA regulates and controls the manufacture, import/export, distribution, research, and possession of controlled substances. These controls, as well as civil and criminal sanctions for violations of the Act, are generally keyed to a product's scheduling status, although certain penalties attach to specific substances, such as cannabis. 21 U.S.C. sec. 841. The CSA reaches down to the ultimate user, making it unlawful to possess any controlled substance without a valid prescription. 21 U.S.C. sec. 844. A valid prescription can only be issued by a practitioner with authority to dispense the drug, 21 U.S.C. sec. 353(b), and, as noted above, only products approved by the FDA may be prescribed by practitioners and dispensed by pharmacists. The U.S. Supreme Court has determined that the CSA may prohibit the intrastate, noncommercial manufacture and possession of controlled substances for personal medical use. *Gonzales v. Raich* (2005) 545 U.S. 1.

The CSA permits States to impose equivalent restrictions under their own laws. Many states have adopted the Uniform Controlled Substances Act,<sup>16</sup> whose provisions parallel those of the federal CSA. States can serve as an early warning system, and have the flexibility to respond more quickly to new or increasing abuses of controlled substances -- or of uncontrolled substances with abuse potential -- within their borders.<sup>17</sup> The CSA therefore also permits States to enact additional requirements or restrictions that are more stringent than those set forth in the CSA. For example, as an added layer of protection, states

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<sup>13</sup> The FDCA maintained significant control over controlled substances until 1968, when all federal drug control was consolidated under the Department of Justice. The Drug Abuse Control Amendments of 1965 (DACA), Pub.L.89-74, July 15, 1965, 79 Stat. 226, 21 U.S.C. sec. 360a, which were founded on the Commerce Clause, imposed restrictions and prohibitions on the intra- or interstate manufacture, sale, delivery, disposal, or possession of depressants, stimulants, and hallucinogens. *White v. U.S.*, 399 F.2d 813, 822 (8<sup>th</sup> Cir. 1968). Although DACA contained an exception for personal use, by the time of the CSA's enactment, the United States was obliged by the Single Convention to extend its system of controls to local/individual manufacture, possession and use of controlled substances.

<sup>14</sup> However, if control is required by the United States' obligations under international treaties, the Attorney General must issue an order controlling the drug under the schedule he/she deems most appropriate to carry out such obligations, without regard to any of the findings described above. 21 U.S.C. sec.811. See further discussion of U.S. international treaty obligations below.

<sup>15</sup> *Grinspoon v. DEA*, (1st Cir. 1987) 828 F.2d 881,890, citing H.R. Rep. No. 534, 98<sup>th</sup> Cong. 2d Sess. 4 (1984), reprinted in 1984 U.S. Code Cong. & Admin. News 540,543. However, rescheduling of a Schedule I substance (such as cannabis) would not alone be sufficient to create a medication that physicians could prescribe and pharmacists could dispense. In order to be prescribable, any particular medication must have successfully completed the FDA approval process. The FDA does not approve "bulk" substances, such as cannabis (or raw opium or coca leaves), for marketing and direct prescription. Therefore, a specific cannabis-derived product would have to be developed in accordance with FDA standards, which would require that it be standardized, formulated, tested, and administered in an appropriate delivery system.

<sup>16</sup> See, National Conference of Commissioners on Uniform State Laws.

[http://www.nccusl.org/nccusl/uniformact\\_summaries/uniformacts-s-ucsa90.asp](http://www.nccusl.org/nccusl/uniformact_summaries/uniformacts-s-ucsa90.asp). Calif. Health & Safety Code §§11000-11651.

<sup>17</sup> For example, *Salvia divinorum* (whose active constituent is salvinorin A) is an 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](http://www.deadiversion.usdoj.gov/drugs_concern/index.html).

may require that individuals who conduct research into controlled substances must be independently inspected, and/or licensed or approved, by state agencies, in addition to obtaining DEA registrations.<sup>18</sup> 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).<sup>19</sup> State or local legislation or other regulatory action cannot, however, contravene the provisions of the CSA.<sup>20</sup>

### **International Treaty Obligations Require the United States to Exert Plenary Control over the Domestic Manufacture, Distribution, Import/export, and Possession of, as well as International Trade in, Substances with Abuse Potential.**

International treaty obligations mandate that the U.S. exert extensive and strict controls over substances with abuse potential. The U.S. is a signatory to several international drug control treaties. See, e.g., the 1961 Single Convention on Narcotic Drugs (Single Convention), 18 U.S.T. 1407 (1967), 520 U.N.T.S. 151 (1964), and the 1971 Convention on Psychotropic Substances (1971 Convention), 1019 U.N.T.S. 175 (1976), Treaty No. 14,596.<sup>21</sup> The CSA was enacted in part to implement the U.S.’s obligations under those conventions. Congressional findings reflect that fact. 21 U.S.C. secs. 801(7), 801a. These treaties require the Parties to impose certain restrictions and controls on domestic manufacture, distribution, import/export, and possession of, and international trade in, controlled substances. One fundamental principle animates the fabrics of the treaties: the production and use of narcotic drugs and scheduled psychotropic substances must be limited exclusively to medical and scientific purposes. 1961 Convention, preamble, Art. 4(c). See also, 1971 Convention, preamble, Art. 5.

The treaties recognize that, while addiction to narcotic drugs and the misuse of scheduled psychotropic substances are serious risks to public health and safety, the proper use of legitimate medical products is essential for the relief of pain and suffering. See, e.g, 1961 Convention, preamble. Accordingly, their provisions were structured to ensure that each Party could make new narcotic-containing medical products available to its citizens in a timely fashion. However, it is clear that, in order to comply with those provisions, a Party must require that the development and approval processes for such medicinal products meet the exacting standards of modern medicine. The CSA was scrupulously crafted to address and implement these requirements, as well as every other aspect of the controls mandated by the treaties.

The treaties were promulgated at a time when governmental regulatory bodies, such as the FDA, were imposing strict controls on the quality and safety of medical products. The need for the practice of medicine to be “evidence-based” had 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,

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<sup>18</sup> The Research Advisory Panel (RAP) of the California Attorney General’s office must approve all Schedule I and II research projects and protocols. Calif. Health & Safety Code §§11480-81. <http://caag.state.ca.us/research>.

<sup>19</sup> DEA, State Prescription Drug Monitoring Programs. [http://www.deadiversion.usdoj.gov/faq/rx\\_monitor.htm](http://www.deadiversion.usdoj.gov/faq/rx_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.

<sup>20</sup> States may place a controlled substance in a schedule under state law that is lower than its classification under the CSA. For example, Ohio and Oregon have rescheduled cannabis to Schedule II under state law. However, such state-level rescheduling merely lessens state-level criminal penalties for illegal use, possession, manufacture, etc. It does not enable the substance to be prescribed by physicians. This is governed by the FDCA and the CSA.

<sup>21</sup> The United States is also a party to the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, which focuses primarily on the means of addressing and controlling international drug trafficking.

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).<sup>22</sup> Nowhere in the treaties is there any suggestion that a Party may allow a diluted or informal “medical” system solely for specific controlled substances, such as cannabis.<sup>23</sup> States may not take actions which have the effect of subverting the ability of the U.S. to fulfill these international treaty responsibilities.

## **Conclusion**

Current cannabis distribution schemes contravene accepted scientific standards and conflict with both federal and international laws governing the development of medications containing substances with abuse liability. Such a blatant circumvention of the FDCA is a dangerous precedent undermining more than a century of public health legislation. The CSA, together with the FDCA, provides an integrated regulatory system to ensure that substances with abuse liability 1) may be incorporated into prescribed medications that have been developed in accordance with strict scientific standards and 2) are manufactured, distributed, and used solely for medical and scientific purposes. Cannabis is the most widely abused drug in the world. The current “medical marijuana” movement encourages the perception that marijuana is not only safe but healthy. This is likely to encourage large increases in nonmedical use, especially among youth. It is therefore particularly essential that these regulatory structures be maintained and supported.

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<sup>22</sup> The Single Convention recognized that different countries may have different regulatory systems. See 1961 Commentary, Art.4, para.12, p. 111 (“legitimate” existing systems of indigenous medicine may be taken into account). However, it contemplated that each Party would employ its conventional regulatory standards when determining whether, and which, narcotic substances and products could be made available for medical use.

<sup>23</sup> Furthermore, at the time of the Single Convention, crude narcotic plant material was not considered suitable for medical use. For example, opium smoking and coca leaf chewing were not accepted methods for delivering the therapeutically useful components contained within the herbal material. Only processed and refined botanical extracts could constitute a medicinal product.<sup>23</sup> Indeed, by the 1850s, the medicinal use of pure alkaloids, rather than crude opium preparations, was common in Europe. Department of Justice, Drug Enforcement Administration, “Opium Poppy Cultivation and Heroin Processing in Southeast Asia,” (March 2001) at p. 2, [www.usdoj.gov/dea/pubs/intel/20026/20026.html](http://www.usdoj.gov/dea/pubs/intel/20026/20026.html) (accessed July 28, 2004) (hereafter “DEA Opium Report”).