DEPARTMENT OF HEALTH AND HUMAN SERVICES

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STATEMENT

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BEFORE THE

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U.S. HOUSE OF REPRESENTATIVES

"Mixed Signals: The Administration's Policy on Marijuana—Part Four—the Health Effects and Science"

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INTRODUCTION

Mr. Chairman, Ranking Member Connolly, and Members of the Subcommittee, I am Dr. Douglas Throckmorton, Deputy Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the important role that FDA plays in the regulation of researching marijuana for potential medical uses in the United States, as part of FDA's mission to protect and promote the public health by ensuring the safety, efficacy, and quality of medical products, including drugs.

I would like to discuss two aspects of the work FDA does related to the regulation of marijuana. First, FDA plays a critical role in regulating the development and potential use of marijuana and its constituents as prescription drugs in the United States. Second, FDA plays a critical role, alone and in partnership with other Federal agencies, in supporting the efficient and scientific assessment of marijuana and its constituents to support needed drug development. Both of these activities are critical if safe and effective drugs are to be developed from marijuana. FDA continues to believe that the drug approval process represents the best way to ensure that safe and effective new medicines from marijuana are available as soon as possible for the largest numbers of patients, and it is important and appropriate to apply these same scientific standards to the development and assessment of any therapeutic uses of marijuana.

FDA's Role in Regulating Marijuana as a Potential Prescription Drug

The first role for FDA in the regulation of marijuana as a potential prescription drug relates to our larger responsibility for the regulation of all drugs intended for human use. The Agency reviews drug product applications to determine whether drugs are safe and effective for their

intended uses. Any product that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease is classified by FDA as a drug. This applies, regardless of the product's form and the way in which the manufacturer chooses to market and label the product.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that drugs be shown to be safe and effective for their intended uses before being marketed in the United States. In approving a drug for marketing, FDA reviews important information about the drug, including:

1. The indication for which the drug has been shown to be effective at treating, including specific uses in children or the elderly, if any
2. What patients may benefit from its use, including information about whether the drug has been tested in children
3. What adverse effects have been reported for individuals taking the drug
4. How the drug should be taken (*e.g.*, orally, intravenously)
5. The dose of the drug that is recommended to be used
6. How the drug is made (*e.g.*, as a pill, liquid) and what is in the drug, including both active and inactive ingredients

Getting a drug approved requires the collection and submission to FDA of clinical and non-clinical data about the proposed use of the drug for review as part of a New Drug Application (NDA) or Biologics License Application (BLA). Usually, the first step that a sponsor takes to obtain approval for a new drug is to use non-clinical tests to determine drug toxicity. The sponsor then takes those testing data, along with additional information about the drug's composition and manufacturing, to develop a plan for testing the drug in humans. The sponsor then submits these data to FDA in the form of an Investigational New Drug (IND) application

that includes protocols describing proposed studies, the qualifications of the investigators who will conduct the clinical studies, and assurances of informed consent and protection of the rights, safety, and welfare of the human subjects. FDA then reviews the IND to ensure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate assurances of informed consent and human subject protection. At that point, the drug testing in humans can begin.[1]

Briefly, the initial clinical trials assess how to safely administer and dose the drug when used in small numbers of healthy volunteers. If those trials are successful, later studies explore the effectiveness of the drug for a particular indication over a range of doses and determine short-term side effects. These studies typically involve a few hundred subjects. If later studies are successful, pivotal studies are then designed to build on the information learned in the earlier studies to further study safety and assess the efficacy of the investigational drug for a particular indication in a defined patient population. These studies can also provide additional safety data, including long-term experience effects of the drug in certain patient groups, and efficacy of different doses of the drug. These later trials can sometimes enroll several thousand subjects to provide the needed information about the investigational drug's safety and efficacy. Following the completion of these studies, the data might be submitted to FDA as an NDA or BLA for the Agency to review. Throughout the development process, FDA strongly encourages sponsors to work closely with the Agency to support efficient drug development.

In addition to establishing the safety and efficacy of the investigational drug, manufacturers also must demonstrate that they are able to consistently manufacture a high-quality drug product.

[1] In the case of controlled substances, practitioners must first register with the Drug Enforcement Administration before proceeding with clinical trials using controlled substances. Registration requirements applicable to Schedule I controlled substances differ from those for drugs controlled in Schedules II-V (21 U.S.C. 823(f)).

This is an essential part of drug development and presents special challenges when the drug is derived from a botanical source, such as marijuana. Botanicals include herbal products made from leaves, roots, stems, seeds, pollen or any other part of a plant. Botanical products pose challenges that are unique to this class of product, including lot-to-lot consistency. These unpurified products, which may be either from a single plant source or from a combination of different plant substances, can have effects through mechanisms that are either unknown or undefined, making it difficult to determine if the product is causing the change in a patient's condition, or the change is related to some other factor. For these reasons, a focus of drug development from botanicals is identifying a source that will provide the necessary assurance of consistent quality, lot-to-lot. To support development of drugs derived from botanical sources, FDA has released guidance providing information on the development and approval of such drugs that addresses these issues as well as providing more general recommendations on studying botanicals.[2]

Another important consideration is the need to identify a method to consistently provide a given dose of a drug. When the Institute of Medicine (IOM) reviewed the clinical use of marijuana, it identified the problems associated with obtaining consistent dosing using smoked products and recommended that clinical trials involving marijuana should be conducted with the goal of developing safe, alternative delivery systems:[3]

> "If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, 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."

[2] FDA guidance document on the development of botanical drug products: *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf* .
[3] IOM Report, p. 11 (1999), *Marijuana and Medicine: Assessing the Science Base.*

Another consideration related to the regulation of marijuana as a potential medicine is its status as a controlled substance. Under section 202 of the Controlled Substances Act (CSA), marijuana is currently listed as a Schedule I controlled substance.[4] Schedule I includes those substances that have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision.[5] Nevertheless, Schedule I substances, including drugs that are derived from botanical sources such as marijuana, can be and are the subject of clinical trials under the FD&C Act, provided, among other things, that the sponsor successfully submits an IND to FDA and successfully registers with the Drug Enforcement Administration (DEA).[6]

Through the drug development processes described above, FDA has approved two drugs for human use which contain active ingredients that are present or similar to those present in botanical marijuana: Marinol and Cesamet. FDA approved Marinol Capsules in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who had failed to respond adequately to conventional antiemetic treatments. Marinol Capsules include the active ingredient dronabinol, a synthetic delta-9-tetrahydrocannabinol, or THC, which is a psychoactive component of marijuana. Marinol Capsules were approved in 1992 for the treatment of anorexia associated with weight loss in patients with AIDS. FDA approved Cesamet Capsules for the treatment of nausea and vomiting associated with chemotherapy in 1985. Cesamet Capsules contain the synthetic cannabinoid nabilone as the active ingredient.

[4] 21 U.S.C. 812
[5] 21 U.S.C. 812(b)(l)(A)-(C)
[6] 21 U.S.C. 823(f) (stating that registration applications by practitioners wishing to conduct Schedule I research shall be referred by the Secretary of HHS, who shall determine the qualifications and competency of each practitioner, as well as the merits of the research protocol); *see also* 21 CFR 1301.18 (outlining specific application procedures and information to be provided by Schedule I researcher applicants).

These products have undergone FDA's rigorous approval process and have been determined to be safe and effective for their respective indications, and reflect the views of the IOM that the future of marijuana as a potential medicine lies in classical pharmacological drug development.[7] As a result, patients who need medication can have confidence that any approved drug will be safe and effective for its indicated uses.

FDA's Role Under the CSA With Regard to Marijuana

An additional role for FDA in the regulation of marijuana is in making scientific recommendations about the appropriate controls for controlled substances. Under the CSA, controlled substances are listed in one of five schedules, depending on their abuse potential, among other criteria. As noted above, marijuana is currently listed as a Schedule I substance, due not only to its high abuse potential, but also because it currently has no accepted medical use in treatment within the United States and lacks accepted safety for use under medical supervision.

While DEA is the lead Federal Agency responsible for regulating controlled substances and enforcing the CSA, HHS has a number of responsibilities under the CSA, several of which are performed by FDA on behalf of HHS. As a part of this work, FDA provides scientific recommendations to HHS about the appropriate controls for controlled substances, including marijuana. To make this recommendation, CDER, including the Controlled Substance Staff (CSS), is responsible for preparing the "eight-factor analysis" that serves as the basis for the scheduling recommendation to HHS and DEA. This analysis includes the following areas of assessment with regard to a drug or other substance: (1) its actual or relative potential for

[7] Institute of Medicine, Marijuana and Medicine: Assessing the Science Base (IOM Report), p.193 (2003).

abuse;[8] (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history or current pattern of abuse; (5) the scope, duration, and significance of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled under the CSA.[9]

At the request of DEA, in 2001[10] and again in 2006,[11] FDA conducted a review of the available data for marijuana, analyzed the eight factors, and recommended that marijuana remain in Schedule I[12] because of its high potential for abuse, the fact that it has no currently-accepted medical use in treatment in the United States, and because it lacks accepted safety for use under medical supervision.[13]

If an NDA is submitted to FDA for a drug that FDA believes may require rescheduling (*e.g.*, from Schedule I to Schedule II), FDA, working with NIDA and the Assistant Secretary of Health in HHS, prepares a scientific analysis, including a recommendation for scheduling (as discussed above). This analysis is based in part on a review of data on abuse potential submitted by the applicant. The recommendation on scheduling is transmitted from HHS to DEA, which makes

[8] The term "abuse" is not defined in the CSA; however, the legislative history of the CSA suggests the following factors, which FDA considers in determining whether a particular drug or substance has a potential for abuse: (a) individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community; (b) there is a significant diversion of the drug or substance from legitimate drug channels; (c) individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances; and (d) the substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance; thus, making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community. (The Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in U.S.C.C.A.N. 4566, 4603.

[9] 21 U.S.C. 811(c).

[10] *66 Federal Register 20038 (April 18, 2001)*

[11] *76 Federal Register 40552 (July 8, 2011)*

[12] Once the recommendation is completed by FDA, it is then forwarded to the National Institute on Drug Abuse (NIDA) and then to HHS, which, in turn, makes a final recommendation to DEA. The HHS scheduling recommendation is binding on DEA as to scientific and medical matters. Once HHS has transferred to DEA a scheduling recommendation, where the recommendation is to add a drug to a schedule or to transfer a drug to another schedule, DEA goes through a rulemaking process to schedule the drug.

[13] See 74 FR 40552; 66 FR 20038.

the final determination of the appropriate schedule for the substance by scheduling the substance through the rulemaking process prescribed by statute.[14]

FDA's Role in Investigations and Enforcement Actions With Regard to Controlled Substances

In addition to its role in scheduling drugs, FDA sometimes works with the Department of Justice (DOJ), including DEA, and other state and Federal agencies on criminal investigations involving the illegal sale, use, and diversion of controlled substances. FDA recognizes that DEA is the lead Federal Government Agency for enforcement matters related to the diversion of controlled substances, including marijuana. Historically, FDA has deferred to DEA regarding the illegal sale and use of illicit drugs of abuse that have no currently-accepted medical use (*i.e.*, Schedule I drugs).

At present, more than 20 states and the District of Columbia have passed legislation to provide for medical use of marijuana and its derivatives, and several others are considering whether to do so.

FDA's Role in Supporting Development of New Therapies

FDA also plays a role in supporting the development of new drugs, including drugs derived from marijuana and its constituents. This role broadly affects all of drug development. Because of FDA's role as both a regulator and as a public health agency, FDA has a unique perspective on drug development, a perspective we use to identify and facilitate the development of new, innovative products to meet the needs of patients and the American public. We recognize that

[14] *See* 21 U.S.C. 811.

many scientific discoveries still need to be translated into treatments while patients are urgently waiting for new lifesaving therapies, and FDA is committed to helping bridge this gap.

As a part of this activity to streamline drug development, FDA has been actively scrutinizing, strengthening, and streamlining our regulatory processes at various steps along the path from drug discovery to delivery—including the clinical development phase, the longest and most expensive period of drug development. We have developed and successfully used a number of flexible and innovative approaches to expedite the development and review of drugs—to the benefit of millions of American patients. For instance, in 2013, almost three quarters (74 percent) of the 27 new molecular entities approved by FDA were approved first in the United States before any other country.[15]

FDA has four programs that facilitate and expedite development and review of new drugs that address unmet medical needs in the treatment of serious or life-threatening conditions, including Fast Track,[16] Accelerated Approval,[17] Priority Review,[18] and Breakthrough Designation.[19] A look at recent drug approvals suggests that these programs have played an important role in

[15] "President's Fiscal Year 2015 Budget Request for the FDA" Testimony of Commissioner Margaret Hamburg before the Senate Committee on Appropriations (April 3, 2014) at *http://www.fda.gov/newsevents/testimony/ucm392262.htm*.

[16] Fast-track designation: Providing for more frequent meetings and communications with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, including such things as the design of the proposed clinical trials and use of biomarkers.

[17] Accelerated Approval**:** Basing approval not on a clinical endpoint but on an agreed-upon surrogate marker that is a measure, such as blood test or urine marker that is believed to be indicative of a disease state and treatment effect, but not demonstrative of a direct health gain to the patient.
Since its inception in 1992, more than 80 new products have been approved under the Accelerated Approval pathway. It has long been successful in driving innovation in cancer and HIV therapies, but we are encouraging its broader application in other areas, helped by the Food and Drug Administration Safety and Innovation Act (FDASIA), which clarified that FDA has the authority to consider epidemiologic, pharmacologic, or other evidence developed using biomarkers or other scientific methods or tools in determining whether an endpoint can support accelerated approval.

[18] Priority Review**:** Acting on drug applications within six months instead of 10 months for standard review

[19] Breakthrough Therapy designation**:** Providing all of the benefits of Fast-Track designation plus intensive guidance on an efficient drug development program, beginning as early as Phase 1, and the commitment from FDA's review staff, including senior managers, to work closely together throughout the drug development and review process. FDA's new Breakthrough Therapy Designation, was created as part of the 2012 FDA Safety and Innovation Act (FDASIA) As of May 5, 2014, FDA received 186 requests for designation, and granted 48. Six drugs have been approved, including a late-stage lung cancer drug that was approved—four months ahead of its goal date, using evidence from a trial with 163 patients.

bringing innovative drugs to market. Nearly half of the 27 novel drugs approved by FDA last year took advantage of at least one of these expedited drug development and review approaches.

Development programs for drugs derived from marijuana are eligible for these expedited review and development programs under appropriate circumstances, and some are being used to aid the development of drugs derived from marijuana. For example, in April 2014, GW Pharmaceuticals announced that FDA granted Fast-Track designation[20] to its investigational drug product Sativex®, composed primarily of two cannabinoids: CBD (cannabidiol) and THC, administered as a metered-dose oromucosal spray, for the treatment of pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy. Sativex is currently in Phase 3 clinical trials for this indication. In addition, on June 6, 2014, GW Pharmaceuticals announced that FDA granted Fast-Track designation to its investigational CBD product, Epidiolex®, in the treatment of Dravet syndrome, a rare and catastrophic treatment-resistant form of childhood epilepsy.[21]

FDA also understands the interest in making investigational products available to patients while they are being studied for approval, and there are expanded access provisions in both FDA's statute and its regulations to make this possible. FDA's expanded-access mechanisms are designed to facilitate the availability of investigational products to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy available, either because the patients have exhausted treatment with or are intolerant of approved therapies, or when the patients are not eligible for an ongoing clinical trial.[22] FDA

[20] *http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20that%20Sativex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20in%20Cancer%20Pain.aspx*
[21] *http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Epidiolex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20for%20the%20Treatment%20of%20Dravet%20Syndrome.aspx*
[22] *http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm177138.htm*

cannot mandate or require a drug company to provide an unapproved drug to patients, and the availability of an investigational product through expanded access depends on the agreement of the drug company to make the drug available for the expanded access use, either through the company's own expanded access program or to a treating physician for administration to his or her patient.

The expanded access program is being used in the area of marijuana. Epidiolex, containing CBD, is being developed for the treatment of certain seizure disorders in children.[23] GW Pharmaceuticals has announced that there are now 21 active expanded access INDs for Epidiolex treating approximately 300 patients with epilepsy syndromes. Approximately 95 percent of these INDs are for patients between 1 and 17 years of age.[24]

FDA is working with researchers, who are conducting studies on the development of new drugs derived from marijuana, meeting with them regularly as they plan and carry out the trials as a part of their INDs. Although marijuana is a Schedule I substance, it can be, and is being, used in clinical trials, provided that the sponsor submits an IND and registers with DEA. A number of government-funded research projects involving marijuana or its component compounds have been completed or are currently in progress, many of which are listed on the *ClinicalTrials.gov* website. NIDA also permits and funds studies on potential therapeutic benefits of marijuana or its constituent chemicals and lists such studies on its website.[25]

[23] Epidiolex received orphan product designation for treatment of Dravet syndrome. *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=409313* and more recently for treatment of Lennox-Gastaut syndrome: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=421213*

[24] *http://www.gwpharm.com/Epidiolex.aspx*

[25] *http://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-therapeutic-benefits-cannabis-cannabinoids*.

As a part of encouraging appropriate research into marijuana and its constituents, FDA has also worked with investigators to provide clear information on how to conduct research in this area. To help address common questions about research into marijuana, FDA, NIDA, and DEA all have created materials online to help researchers.[26] We also know that a number of states are interested in allowing access to cannabinoid oil, or CBD, to treat childhood epilepsy. FDA encourages and supports medical research into the safety and effectiveness of marijuana products through adequate and well-controlled clinical trials conducted under an IND and consistent with DEA requirements for research on Schedule I substances. FDA has talked with representatives from several states that are considering support for medical research of marijuana and its derivatives to provide scientific advice and to help ensure that their research is rigorous and appropriate. For example, Georgia Governor Nathan Deal recently announced that Georgia Regents University-Augusta is planning to conduct clinical trials of Epidiolex.[27] Also, Governor Andrew M. Cuomo announced an agreement between New York State and GW Pharmaceuticals to develop clinical trials using Epidiolex to help treat children diagnosed with epilepsy who suffer from seizures and other medical complications.[28]

Collaboration with Other Agencies

Another role FDA plays in the regulation of marijuana for potential medical use is our work to support scientific advances related to drug abuse with our sister agencies. FDA and other Federal agencies, including DEA and NIDA, work together on several issues related to marijuana. For example, as described above, FDA works with NIDA and DEA as a part of drug

[26] *http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm362986.htm*; *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf* ; "Guidance for Industry: Botanical Drug Products" at *http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070491.pdf.http://www.drugabuse.gov/drugs-abuse/marijuana/marijuana-research-nida*; *http://www.deadiversion.usdoj.gov/drugreg/faq.htm#sched1*

[27] *http://gov.georgia.gov/press-releases/2014-04-10/deal-leads-state-path-forward-cannabis-oil-treatment*

[28] *http://www.governor.ny.gov/press/06032014-new-medical-treatments*

scheduling. FDA sometimes works with the Department of Justice (DOJ), including DEA, and other state and Federal agencies on criminal investigations involving the illegal sale, use, and diversion of controlled substances. FDA and NIDA also participate in meetings with the Office of the National Drug Control Policy, along with DEA. Finally, FDA participates in the interagency work group that the HHS Office of the Assistant Secretary for Health coordinates to review non-federally funded scientific research proposals that require the use of research-grade marijuana. This committee is composed of a number of HHS agencies, as relevant to the topic of the research, and routinely includes individuals from FDA, NIDA, other NIH components, and the Substance Abuse and Mental Health Services Administration.

CONCLUSION

FDA appreciates this opportunity to discuss FDA's work in the regulation of marijuana for potential medical uses in the United States, which is a part of FDA's larger mission to protect and promote the public health by ensuring the safety, efficacy, and quality of medical products, including drugs. There is considerable public interest in developing new therapies from marijuana and its constituents. FDA will continue to support development of such new therapies that are safe, effective, and manufactured to a high quality, applying the drug development paradigm that continues to provide important new medicines for patients. This paradigm, grounded in rigorous scientific research, is essential to determining the appropriate uses of marijuana and its constituents in the treatment of human disease. As a part of this important work, we are committed to collaborating with Federal and state agencies, researchers, and manufacturers also working on issues related to the use of marijuana in the United States, including cooperation to help speed the development of safe and effective new drugs. Thank you for your interest in this important topic, and I am happy to answer any questions.

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Dr. Throckmorton has been at the FDA since 1997. He received his training in Internal Medicine and Nephrology from the University of Nebraska Medical School, Case Western Reserve University and Yale University. Prior to coming to the FDA he was a basic science researcher and academic physician at the Medical College of Georgia and the Veterans Administration Hospital in Augusta Georgia.