DEPARTMENT OF HEALTH AND HUMAN SERVICES

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STATEMENT

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BEFORE THE

CAUCUS ON INTERNATIONAL NARCOTICS CONTROL

U.S. SENATE

"Cannabidiol: Barriers to Research and Potential Medical Benefits"

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INTRODUCTION

Chairman Grassley, Co-Chairman Feinstein, and Members of the Caucus, I am Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs at the Center for Drug Evaluation and Research (CDER), 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, including its constituent compounds, such as cannabidiol, for potential medical uses. This is an important part of FDA's mission to protect and promote the public health by helping to ensure the safety, efficacy, and quality of medical products, including drugs. In addition, I will briefly discuss the regulatory oversight function of the Agency with respect to other products that may contain cannabidiol.

FDA plays a critical role in regulating the development and potential use of cannabidiol and other constituents of marijuana as prescription drugs in the United States. FDA also, on its own and in partnership with other Federal agencies, supports the efficient and scientific assessment of cannabidiol and other constituents of marijuana in drug development. These activities are critical, if safe and effective drugs are to be developed from marijuana, including from its constituent components such as cannabidiol. FDA continues to believe that the drug approval process represents the best way to help ensure that safe and effective new medicines, including any such medicines derived from cannabidiol or other constituents of marijuana, are appropriately reviewed for safety and effectiveness, consistent with FDA's statutory requirements. It is important and appropriate to use the same scientific standards in the development and assessment of potential therapeutic uses of cannabidiol as with any unapproved drug that the Agency reviews.

FDA's Role in Reviewing Cannabidiol as a Potential Prescription Drug

The role of FDA in the regulation of cannabidiol 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 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, the product's active or inactive ingredients, or the way in which the manufacturer chooses to market and label the product.

In approving a drug for marketing, FDA reviews important information about the drug, including:

1. The indication for which the drug has been studied, including specific uses in children or the elderly, if any
2. Which 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 recommended in the intended patient populations
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 test the drug in animals to determine drug toxicity. The sponsor uses those animal data, along with additional information about the drug's composition and manufacturing, to develop a plan for testing the drug in humans. The sponsor submits the animal data to FDA in the form of an Investigational New Drug (IND) application that includes protocols describing proposed human 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 participants. FDA reviews the IND to confirm that the proposed studies, generally referred to as clinical trials, do not place human participants at unreasonable risk of harm. FDA also verifies that there are adequate assurances of informed consent and human subject protection. At that point, drug testing in humans can begin.[1]

Typically, the initial clinical trials (Phase 1) assess how to safely administer and dose the drug when used in small numbers of healthy volunteers. If Phase 1 trials are successful, Phase 2 studies explore the effectiveness of the drug for a particular indication, over a range of doses, and determine short-term side effects. If Phase 2 studies are successful, pivotal Phase 3 studies are designed based 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. Phase 3 studies also can 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 sometimes enroll several hundreds to thousands of participants—depending on the indication studied—to provide essential information about the investigational drug's safety and efficacy.

[1] In the case of Schedule I controlled substances, such as marijuana from which cannabidiol is derived, the Controlled Substances Act requires researchers to register with the Drug Enforcement Administration (DEA) before handling the controlled substances, including proceeding with clinical trials using controlled substances. Registration requirements applicable to research involving Schedule I controlled substances differ from those for drugs controlled in Schedules II-V (21 U.S.C. 823(f)).

Following the completion of these studies, the data might be submitted to FDA in 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. 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 unknown or undefined mechanisms, 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 for botanicals is identification of 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 potential clinical use of marijuana, it identified the problems associated with obtaining consistent dosing using smoked

[2] FDA guidance document on the development of botanical drug products is posted at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf*.

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.

Another consideration related to the regulation of cannabidiol as a potential medicine is its status as a constituent of a controlled substance, in this case marijuana. 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 such as marijuana, can be and are the subject of clinical trials under the Federal Food, Drug and Cosmetic Act (FD&C Act), provided, among other factors, that FDA authorizes an IND application submitted by a sponsor. In addition, the CSA requires researchers to register with the Drug Enforcement Administration (DEA) before handling Schedule I controlled substances, including conducting clinical trials.[6]

Through the drug development processes described above, FDA has approved two drugs for human use which contain synthetic cannabinoids: Marinol (Schedule III) and Cesamet (Schedule II). 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 existing

[3] IOM Report, p. 11 (1999), *Marijuana and Medicine: Assessing the Science Base*.
[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 to 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).

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 also 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.

These products have undergone FDA's rigorous approval process and have been determined to be safe and effective for their respective indications and dosing, and demonstrate 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 in Supporting Development of New Therapies

FDA also plays a role in supporting the development of new drugs. 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 many scientific discoveries still need to be translated into treatments, even as 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

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

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 2014 almost two-thirds (26 of 41, 63 percent) of new molecular entities approved by CDER were approved in the United States before any other country.[8] This is comparable to the previous year, 2013, in which almost three-quarters of CDER-approved new molecular entities (74 percent of 27) were approved first in the United States.[9]

FDA has several programs that directly facilitate and expedite development and review of new drugs that address unmet medical needs in the treatment of serious or life-threatening conditions: Fast Track,[10] Accelerated Approval,[11] Priority Review,[12] and Breakthrough Designation.[13] A look at recent drug approvals in CDER suggests that these programs have played an important role in bringing innovative drugs to market. Nearly half of the 27 novel drugs approved by CDER in 2013 took advantage of at least one of these expedited drug development and review

[8] CDER Report, "*Novel new Drugs, 2014 Summary*," (1/14/15) is posted at *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf*

[9] "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*.

[10] Fast-track designation: Provides opportunities for frequent interactions 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.

[11] Accelerated Approval**:** Basing approval on an agreed-upon surrogate marker that is a measure, such as a 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, or on an intermediate clinical endpoint likely to predict clinical benefit. Since its inception in 1992, 89 original new drug or biologic applications have been approved in CDER 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 2012 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.

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

[13] 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 FDASIA. As of May 29, 2015, CDER received 258 requests for designation, and granted 78. As of May 29, 2015, 24 drug development programs designated breakthrough have been approved by CDER. Of these 24, 14 were for original applications and 10 were for supplements (to expand or add a new indication to an already approved drug).

approaches. Utilization of these accelerated programs was even more pronounced in 2014, with two-thirds (27 of 41) of novel drugs approved by CDER using at least one of these programs.

Development programs for drugs derived from marijuana and its constituents, including cannabidiol, may be eligible for these expedited review and development programs under appropriate circumstances and, in fact, some of these programs are currently being used in the development of such drugs. For example, in April 2014, GW Pharmaceuticals announced[14] that FDA granted Fast-track designation to its investigational drug product Sativex®, composed primarily of two cannabinoids: 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. GW Pharmaceuticals has announced[15] that Sativex is currently in Phase 3 clinical trials for this indication. In addition, on June 6, 2014, GW Pharmaceuticals announced[16] that FDA granted Fast-track designation to its investigational cannabidiol product, Epidiolex®, in the treatment of Dravet syndrome, a rare and catastrophic treatment-resistant form of childhood epilepsy. In February 2015, Insys Therapeutics announced[17] that FDA granted Fast-track designation to the cannabidiol formulation they are studying for the same condition.

As it does in other new drug development processes, FDA is working with researchers who are conducting studies on the development of new drugs derived from marijuana, including from its constituents such as cannabidiol, 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

[14] *http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20that%20Sativex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20in%20Cancer%20Pain.aspx*
[15] http://www.gwpharm.com/Third%20phase%20III%20Sativex%20cancer%20pain%20trial%20commences.aspx
[16] *http://www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Epidiolex%20Receives%20Fast%20Track%20Designation%20from%20FDA%20for%20the%20Treatment%20of%20Dravet%20Syndrome.aspx*
[17] *http://www.insysrx.com/investors/recent-news/* (Link at February 26, 2015)

being, used in clinical trials conducted under INDs. A number of government-funded research projects involving marijuana or its component compounds, including cannabidiol, have been completed or are currently in progress, many of which are listed on the *www.ClinicalTrials.gov* website.

FDA also understands the interest in making investigational products available to patients while being studied for approval, and there are expanded access provisions in both FDA's statute and its regulations to make this possible, where appropriate and where the manufacturer chooses to participate. 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 because the patients are not eligible for an ongoing clinical trial.[18] FDA 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 a patient or patients.

As noted, Epidiolex, containing cannabidiol, is being developed for the treatment of certain seizure disorders in children.[19] GW Pharmaceuticals reports that 20 Epidiolex intermediate-size expanded access INDs have been authorized to treat approximately 420 children and that

[18] *http://www.fda.gov/ForPatients/Other/default.htm*

[19] 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 the treatment of Lennox-Gastaut syndrome: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=421213*

approximately 95 percent of Epidiolex expanded access INDs are for patients between 1 and 17 years of age.[20]

FDA also has worked with investigators to provide clear information on how to conduct research in this area. To help address common basic questions about research with marijuana, FDA, the National Institute on Drug Abuse (NIDA), and DEA have posted materials online to help researchers.[21] We also know that a number of states are interested in allowing access to cannabidiol-containing oils to treat childhood epilepsy. FDA encourages and supports medical research into the safety and effectiveness of products containing cannabidiol and other marijuana constituents 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 considering support for medical research of marijuana and its derivatives, including cannabidiol, to provide scientific advice and to help ensure that their research is rigorous and appropriate.

FDA's Role in Investigations and Enforcement Actions With Regard to Products Containing Cannabidiol

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, such as Schedule 1 drugs, which have no currently accepted medical use.

[20] *http://www.qwpharm.com/Epidiolex.aspx*

[21] *http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm362986.htm;*
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070491.pdf
http://www.drugabuse.gov/drugs-abuse/marijuana
http://www.deadiversion.usdoj.gov/drugreg/faq.htm#sched1

However, in addition to regulating medical products, FDA maintains regulatory oversight over foods, including dietary supplements. For any product found to be in violation of the FD&C Act, FDA considers many factors in deciding whether or not to initiate an enforcement action. Those factors include, among others, Agency resources and the threat to the public health. FDA also may consult with its Federal and state partners in making decisions about whether to initiate a Federal enforcement action.

In late February 2015, FDA issued several Warning Letters to firms that were marketing unapproved drugs for the diagnosis, cure, mitigation, treatment, or prevention of diseases. Some of these firms claimed that their products, which the firms made available nationwide via the Internet, contained cannabidiol which the firms claimed could help to address cancer, diabetes, multiple sclerosis, and other ailments. FDA tested those products and, in some, did not detect any cannabidiol.[22] It is important to note that these products are not approved by FDA for the diagnosis, cure, mitigation, treatment, or prevention of any disease. Often they do not even contain the ingredients found on the label. Although FDA advised these firms that their products were in violation of the FD&C Act, and FDA is committed to keeping violative products off the market, consumers should be extremely cautious in purchasing and using such products. Marketing of products that are not what they claim to be, such as those purporting to contain cannabidiol but don't, does more than simply defraud consumers who anticipate that the products purchased will contain the ingredients expected. These products and marketing can create false hope in a population especially vulnerable: those seeking relief from serious medical conditions for themselves or their loved ones, including their children. Moreover, it might divert patients from products with demonstrated safety and effectiveness.

[22] For information on these warning letters and the product testing, please see *http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm*

The recent examples of the products being marketed to individuals seeking relief from serious medical conditions—products that FDA has not evaluated for safety and efficacy and that often do not even contain the ingredients they claim to contain—serves as another reminder of the important role FDA and the drug approval process play in this area.

CONCLUSION

FDA appreciates this opportunity to discuss the Agency's work in the regulation of cannabidiol for potential medical uses in the United States, which is a part of FDA's core mission to protect and promote the public health by helping to ensure the safety, efficacy, and quality of medical products, including drugs. There is considerable public interest in developing new therapies from marijuana and its constituents, especially cannabidiol. FDA will continue to play its role in ensuring that any such new therapies are safe, effective, and manufactured to a high quality, applying the drug development paradigm that continues to provide new medicines that meet these standards for patients. This paradigm, grounded in rigorous scientific research, is essential to determining any 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 cannabidiol and other constituents of marijuana in the United States. The drug approval process remains the best way to identify new treatments that are safe and effective for patients and to protect patients from products that are not what they purport to be.

Thank you for your interest in this important topic, and I am happy to answer any questions.