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Written Testimony
"Cannabidiol: Barriers to Research and Potential Medical Benefits"

Chairman Grassley, Co-Chairman Feinstein, distinguished members of the Caucus and guests, thank you for providing me with the opportunity to appear before you today to discuss cannabidiol (CBD), and more specifically, its potential medical benefits and barriers to research.

I have studied, researched, and written about drug policy, drug markets, drug prevention, drug treatment, criminal justice policy, addiction, and public policy analysis for 20 years. Most recently, from 2009-2011, I served in the Obama Administration as a senior drug policy advisor. I am currently the co-founder, with former Congressman Patrick J. Kennedy, of SAM (Smart Approaches to Marijuana). I am also the Director of the Drug Policy Institute at the University of Florida and author of *Reefer Sanity: Seven Great Myths About Marijuana.*

I am delighted to share with you my perspective, based on evidence and experience, on cannabidiol's potential medical benefit and practical and responsible ways research can be conducted on its use.

Let me start by saying that although most major medical associations and I vigorously oppose marijuana legalization, it is important to separate the discussion of the recreational use of marijuana and the potential medical benefits of its components. Cannabis is a complex plant with hundreds of constituents; inhaled, on average it contains 14% THC and virtually no CBD. Using today's high THC marijuana, especially for young people, is significantly associated with a reduction in IQ[1], mental illness[2], poor

[1] See Meier, M.H.; Caspi, A.; Ambler, A.; Harrington, H.; Houts, R.; Keefe, R.S.E.; McDonald, K.; Ward, A.; Poulton, R.; and Moffitt, T. Persistent cannabis users show neuropsychological decline from childhood to midlife.*Proceedings of the National Academy of Sciences* 109(40):E2657–E2664, 2012. Also Moffitt, T.E.; Meier, M.H.; Caspi, A.; and Poulton, R. Reply to Rogeberg and Daly: No evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline. *Proceeding of the National Academy of Sciences* 110(11):E980-E982, 2013.

[2] See for example: Andréasson S., et al. (1987). Cannabis and Schizophreia: A longitudinal study of Swedish conscripts. *Lancet, 2*(8574); Moore, T.H., et al. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet, 370*(9584); Large M., et al. (2011). Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis. *Archives of General Psychiatry, 68*(6); Harley, M., et al. (2010). Cannabis use and childhood trauma interact additively to increase risk of

learning outcomes[3], lung damage[4], and addiction.[5] According to the National Institutes of Health, one out of every six adolescents who use marijuana will become addicted[6], and many more will develop some problems as a result of marijuana use. There are about 400,000 emergency room admissions for marijuana every year – related to acute panic attacks and psychotic episodes[7] – and marijuana is the most cited drug for teens entering treatment.[8] The heavy use of marijuana has increased rapidly in the last decade; and it's estimated that the market for marijuana has quadrupled since 1990 ($10B to $40B) while the cocaine market has been cut by half ($30B to $15B) during that same period of time.[9]

But my testimony will not focus on high-THC marijuana. It is important to make that distinction – just as we derive morphine, a useful pain medication, from opium, yet we do not prescribe heroin or smoked opium for pain. Similarly we could imagine deriving active ingredients from the marijuana plant for medicinal use without approving of inhaling marijuana.

Right now the current situation can be summed up this way: Most CBD manufacturers get away with selling whatever they say is CBD; researchers and other groups who want to follow the FDA/DEA rules are being stifled by bureaucracy; parents are left confused and frustrated; FDA approved CBD products could very well be held up through a lengthy DEA scheduling process; and

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psychotic symptoms in adolescences. *Psychological Medicine, 40*(10); Lynch, M.J., et al. (2012). The Cannabis-Psychosis Link. *Psychiatric Times.*

[3] Yucel, M., et al. (2008). Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of General Psychiatry, 65*(6).

[4] See for example: American Lung Association. (2012, November 27). Health Hazards of Smoking Marijuana. Retrieved from: http://www.lung.org/stop-smoking/about-smoking/health-effects/marijuana-smoke.html; Tashkin, D.P., et al. (2002). Respiratory and immunologic consequences of smoking marijuana. *Journal of Clinical Pharmacology, 4*(11); Moore, B.A., et al. (2005). Respiratory effects of marijuana and tobacco use in a U.S. sample. *Journal of General Internal Medicine, 20*(1); Tetrault, J.M., et al. (2007). Effects of marijuana smoking on pulmonary structure, function and symptoms. *Thorax, 62*(12); Tan, W.C., et al. (2009). Marijuana and chronic obstructive lung disease.

[5] See for example: Anthony, J.C., Warner, L.A., Kessler, R.C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experiential and Clinical Psychopharmacology, 2*; Budney, A.J., et al. (2008). Comparison of cannabis and tobacco withdrawal: Severity and contributions to relapse. *Journal of Substance Abuse Treatment, 35*(4); Tanda, G., et al. (2003). Cannabinoids: Reward, dependence, and underlying neurochemical mechanisms – A recent preclinical data. *Psychoparmacology, 169*(2).

[6] Anthony, J.C., Warner, L.A., Kessler, R.C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experiential and Clinical Psychopharmacology, 2.*

[7] Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2011). Drug abuse warning network, 2008: National estimates of drug-related emergency department visits. *HHS Publication* No. SMA 11-4618. Rockville, MD.

[8] Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2000-2010. National Admissions to Substance Abuse Treatment Services. DASIS Series S-61, HHS Publication No. (SMA) 12-4701. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012

[9] Kilmer et al. (2014). "How big is the US market for illegal drugs?" RAND Report. Found here http://www.rand.org/pubs/research_briefs/RB9770.html

state elected officials with absolutely no background in these issues are hastily putting laws together in the absence of robust federal action. This must change.

Why CBD now?

A number of years ago, researchers and activists likely inspired by research being conducted by GW Pharmaceuticals in the U.K. (see below), began to educate interested patients and others about the therapeutic potential of CBD, which was virtually absent in high-THC marijuana in the U.S. Indeed, not long ago many individuals in the U.S. believed that CBD was an inert compound. There were also anecdotal reports of some adults with epilepsy who discovered that inhaled marijuana seemed to prevent or reduce their seizures. As more and more scientific research demonstrated that CBD had a variety of therapeutic effects, interest in the use of CBD in epilepsy grew.

The CNN program hosted by Dr. Sanjay Gupta in August 2013 portrayed the case of a little girl with horrible, life-threatening intractable epilepsy. According to Dr. Gupta, her condition was greatly improved by a CBD-rich preparation produced by purveyors in Colorado. Though many were dismayed at how Dr. Gupta's program interchangeably used THC and CBD and further confused the issue of recreational and medical marijuana, the program resulted in enormous interest in CBD from families of children with epilepsy.

As desperate parents sought "high CBD" products wherever they could purchase them, a number of dispensaries and other opportunistic vendors began to sell these products. However, the labeled potency and composition have been found to be often inaccurate and uneven, depending on the marijuana strain from which they come, the methods of manufacture used to prepare them, and the quality of the testing facility/procedures. At many places in the cultivation and manufacturing process, lack of standardization can result in higher levels of THC and lower levels of CBD – as well as the varying levels of dangerous microbes or pesticides--in the final preparation, e.g. growing from seed rather than clones; differences in the cultivation, harvesting, and drying conditions; uneven decarboxylation; and use of toxic extraction chemicals, such as butane or non-pharmaceutical ethanol.

CBD: Big Marijuana Sees An Opportunity

Manufacturers and other purveyors of CBD products make many therapeutic claims that bring those products within the scope of the Food, Drug, and Cosmetic Act (FDCA). For manufacturers of other products such as pharmaceutical products, dietary supplements, and even foods, FDA reviews all sources of promotional statements (including websites, Facebook, Twitter and other online media sources) that could be interpreted as making improper therapeutic claims. **However, with the exception of the very recent past, most medical marijuana companies have been able to conduct business unobstructed.** Claims are made for a wide variety of medical conditions and risks are barely mentioned.

To ensure patient safety, it is important that dosage and composition of CBD products are independently verified and known.[10] FDA has begun to send some warning letters to some CBD companies.[11]

CBD As A Potential Medicine

Despite the clear irresponsible actions of some marijuana businesses, researchers have been interested in exploring the medical potential of CBD. SAM believes that these and similar research initiatives will provide important data regarding the safety and efficacy of CBD. In 1998, recognizing CBD's therapeutic potential, GW Pharmaceuticals incorporated it into their first product, Sativex, a botanically-derived 1:1 CBD to THC ratio. Sativex is now approved for MS spasticity in 27 countries and is completing Phase 3 trials in almost 60 research sites in the US in advanced cancer patients with significant pain. Since 2007, GW has been intensively researching CBD in various medical conditions, including epilepsy. This has ultimately resulted in its investigational, highly purified CBD product, Epidiolex. Pediatric neurologists around the country, concerned that the desperate families of their pediatric patients were seeking access to artisanal CBD preparations of unknown quality and potency, began to seek FDA and DEA approval of expanded access or compassionate access IND programs to treat their patients with intractable epilepsy with Epidiolex. Approximately20 such INDs, covering over 400 children, have been approved by FDA and many have secured DEA research registrations. Physicians with these programs have published data about the benefits and risks of Epidiolex, and the results are very encouraging. GW is also conducting four placebo controlled clinical trials in children with two types of intractable epilepsy. These

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[10] For example, a webpage ad for "Hemp CBD Oil" states that CBD "may have significant medical effects but does not have any psychoactive effects," lists many "common ailments" that can be helped by CBD, including "anxiety or minor pain," cites numerous scientific publications suggesting that CBD can treat many medical conditions, and invites the reader to purchase CBD oil, elixir or gum by clicking on a link http://www.hemp-cbd-oil.com/; http://www.vrgltd.com/ These appear to be products produced by Real Scientific Hemp Oil, and Canchew, subsidiaries of Medical Marijuana, Inc.

[11] Medical claims transform these products into "new drugs" subject to FDA's jurisdiction. FDA's enforcement authority to take action against medical marijuana purveyors exists under several categories, including, at least: (a) misbranding, (b) pre-approval/ off-label advertising and promotion, (c) current Good Manufacturing Practice (cGMP) (d) Manufacturer registration/FDA inspection (e) improper or inadequate labeling or instructions for use; and (f) false and deceptive advertising.

Other manufacturers claim that their CBD products are "nutraceuticals," and legal for sale throughout the U.S.[11] However, at the bottom of one of their webpages, they list various pieces of information and other websites relating to "Colorado Medical Marijuana." The term "medical marijuana" alone would be enough, in any other context (for example, "medical pomegranate juice") to draw FDA[11] attention and enforcement action. Their edible products are "medicated edibles." In addition, these products are sold in "Colorado medical marijuana care centers." Another web page, directed to patients, refers to the "taste and potency you desire from your marijuana medicine…..a grown-up alternative medicine….[p]roviding a 222 mg dose of medicine…." On its Facebook page, it posts an article "focusing on the benefits of CBD," which states in part that CBD "can potentially cure cancer." [11] They also post patient testimonials[11] claiming relief from migraines and back pain. All these promotional statements and materials indicate that their products are intended to be used for the treatment of various medical conditions, thereby bringing them within the misbranding provisions of the FDCA.

trials will take place in 50 research sites in the US. All four of these trials are underway. It is likely that FDA approval could happen by 2017. Then Epidiolex must be rescheduled by DEA before it can be made available by prescription to patients.

Policy Solutions for CBD – What Not to Do

If Congress wanted to allow for the (1) experimental use of CBD before FDA approval and/or (2) increased research on CBD's efficacy, there are some specific things that can be done today by federal regulatory agencies. (If those agencies decided not to utilize these avenues, Congress could pass legislation mandating them to take action.)

Two notably absent recommendations from the list below are (1) rescheduling whole marijuana to Schedule II and (2) descheduling CBD and/or removing CBD from the Food, Drug, and Cosmetic Act (FDCA). Though they may be tempting, these are undesirable potential solutions. If marijuana was rescheduled, as I testified to the U.S. House Government Oversight Committee in 2013, it would do nothing to make marijuana (or CBD) available at pharmacies, it would not legalize marijuana (or CBD) dispensaries in states, and it would not legalize the production or retail sales of marijuana (or CBD). The reason marijuana hasn't been rescheduled is because no *product* of whole, raw marijuana has a "currently accepted medical use" in the U.S., which is part of the legal definition of Schedule I defined by the Controlled Substances Act. By contrast, Schedule II substances have a currently accepted medical use in the U.S. or a currently accepted medical use with severe restrictions. More importantly, regardless of the schedule, *any substance may be prescribed by physicians and dispensed by pharmacists only when incorporated into specific FDA-approved products.* That is why Schedule II opioid products can be obtained in pharmacies by prescription, but **raw opium, despite being in Schedule II, cannot be prescribed.** Rescheduling marijuana is a side issue that has been elevated far above its deserved place in this debate – though it is a focus of the legalization movement because of the powerful symbolism it would provide that movement. For those truly interested in medical and research potential, however, it distracts from the proper issues at hand with regards to CBD. Descheduling CBD or removing it from the FDCA would simply encourage a "free-for-all" of concoctions and mixtures claiming to be "high-CBD" but with absolutely no regulation or oversight. This would result in hazardous conditions for parents and patients. Furthermore, while CBD appears not to have THC-like psychoactivity, there are not yet sufficient data to know whether it has some degree of abuse potential, which might warrant a lower schedule, such as III-V.

Policy Solutions for CBD – A Six Point Plan

Given the increasing interest and demand for research into marijuana's therapeutic potential, Smart Approaches to Marijuana (SAM), a nonpartisan alliance of physicians,

policy makers, prevention workers, treatment and recovery professionals, scientists, and other concerned citizens opposed to marijuana legalization, recently released a new report, *Researching Marijuana's Medical Potential Responsibly*, and called for a series of recommendations. Specifically, the six-point plan recommends the following actions – some falling under the category of **research** and others under the category of **immediate and expanded CBD access for the seriously ill.**

(1) Allow multiple licenses to grow marijuana for research purposes, beyond the sole contractor that works with NIDA

Under international agreements, the National Institute on Drug Abuse is the sole source for research marijuana, which NIDA procures by contract from the University of Mississippi. According to NIDA, demand for marijuana for research purposes is relatively low at this time. Still, multiple states have set up their own marijuana grow operations because of a purported need for marijuana rich in certain components, like CBD. Though the University of Mississippi is now growing marijuana rich in CBD, it is not unreasonable for other NIDA-approved sites to be able to grow different strains of marijuana. Therefore, we endorse the idea of NIDA (or other NIH-entities) to be able to grant multiple contracts for research purposes under strict supervision, in coordination with DEA.

(2) Waive (or lessen) DEA registration requirements for handling CBD

The main reason some researchers have called for rescheduling marijuana altogether is because they have a difficult time working within the DEA registration requirements for handling CBD. There can be long delays between getting FDA approval for handling CBD and checking the boxes to fulfill DEA registration requirements. But this doesn't have to be so. Under the CSA, the DEA has the authority to issue a regulation waiving the registration requirement for certain manufacturers, distributors or dispensers, if the DEA determines that it is "consistent with the public health and safety." 21 USC sec. 822(d). In theory, DEA could waive the Schedule I research registration requirement for physician researchers working under FDA-approved INDs and using products that have met FDA quality standards. Currently, Epidiolex® is currently being fast-tracked by FDA and is showing initial positive data in children with epilepsy being treated in FDA-approved compassionate access IND programs. Each of the physicians with such a program had to go through a burdensome and time-consuming process to secure a Schedule I research registration. Alternatively, since the issuance of a regulation would necessitate publication in the Federal Register, 30 day comment period, and a final rule, perhaps DOJ/DEA could take the route of the recent Cole memo and issue a statement that DEA would issue Schedule I research registrations to all teaching hospitals and clinics with pediatric neurologists and epileptologists, allowing them to possess and dispense purified CBD that has passed some FDA standards. Such registrations could be time-limited, e.g., one year, with a possibility of renewal. If the FDA approves a CBD drug, it then has medical value and must be moved out of Schedule I. At that point, there would no longer be a need for such special registrations.

(3) Eliminate the Public Health Service (PHS) review for marijuana research applications

In 1999, the Department of Health and Human Services (HHS) announced that it intended to establish new procedures "to make available a sufficient amount of research-grade marijuana to support those studies that are the most likely to yield usable, essential data." Marijuana is the only drug that had this new procedure attached to it. HHS explained that "the scientific merits of each protocol will be evaluated through a Public Health Service (PHS) interdisciplinary review process [which] will take into consideration a number of factors, including the scientific quality of the proposed study, the quality of the organization's peer-review process, and the objective of the proposed research." [4] The intention was to streamline and increase research, but the general consensus is that it has had the unintended consequence of discouraging or delaying research. Since research proposals still have to go through FDA and individual Institutional Review Board (IRB) protocols, many have questioned the wisdom of the PHS process, since it seemingly adds an extra step for no reason. Given that research protocols would still need to go through the FDA and other entities, we approve of the recent action eliminating the PHS review process for marijuana research applications.

(4) Establish compassionate CBD research programs for the seriously ill

The CSA authorizes the DOJ/DEA to carry out educational and research programs "directly related to enforcement of the laws…concerning drugs, which may include… (2) studies or special projects to compare the deterrent effects of various enforcement strategies on drug use and abuse; …and (5) studies or special projects to develop more effective methods to prevent diversion of controlled substances into illegal channels….." 21 USC sec. 872 (a).

DOJ/DEA could collaborate with the National Institute for Neurological Diseases and Stroke (NINDS) on a program similar to NCI's Group C program for Marinol. In that program, over 20,000 patients received the drug over a period of four years under a "Group C" program. The Group C program was closed when Marinol was approved. Here's how such a program was described in the 1980s:

> *"The National Cancer Institute (NCI) is initiating a national THC distribution program by applying to the FDA for its classification as a Group C investigational agent. Since THC is also a Schedule I drug, the distribution system requires strict adherence to Drug Enforcement Agency (DEA) security and safety regulations. Contrary to the usual distribution of Group C drugs, THC will not be available directly to physicians. THC will be made available to hospital pharmacies which are: (1) an NCI recognized Cancer Center (P-30 grant supported), (2) an NCI designated New Drug Study Group, (3) a member of the Council of Teaching Hospitals. Hospital pharmacies that are located in inadequately represented geographic areas when certain criteria are met by them will also be considered. Physicians desiring to prescribe THC need not have Schedule I registration, but should (1) have experience in cancer chemotherapy,*

*(2) have a current DEA registration number, (3) agree to abide by the Guidelines for Use of THC, and (4) be registered with a participating pharmacy. A registered physician may prescribe THC by writing a Research Order for Medication on a usual prescription blank, including, in addition to normal required information, confirmation that patient consent has been obtained and the name of the hospital at which the physician is registered to prescribe THC.***"***

(5) Begin federal-state partnerships to allow a pure CBD product to be dispensed/explored by board-certified neurologists and/or epileptologists to appropriate patients under a research program

The federal government could (without the need for changing the CSA) enter into a cooperative agreement with the states. The CSA, 21 USC sec. 873(a), provides:

"The Attorney General shall cooperate with local, State, and Federal agencies concerning traffic in controlled substances and in suppressing the abuse of controlled substances. To this end, he is authorized to….notwithstanding any other provision of law, enter into contractual agreements with State and local law enforcement agencies to provide for cooperative enforcement and regulatory activities under this chapter."

Under this section, the Attorney General is mandated to cooperate and permitted to enter into contractual cooperation agreements "notwithstanding any other provision of law." DOJ could in theory enter into such agreements with state and local agencies in order to expand current research protocols. The argument would be that, by making CBD (that meets FDA quality standards) more available, patients would not have to resort to federally-unlawful channels, such as dispensaries and other purveyors, where they might purchase cannabis with significant amounts of THC; such agreements would thereby "suppress the abuse of controlled substances."

(6) Shut down rogue "medical marijuana" companies that do not play by the rules

While commencing or facilitating a research program for pure prescription-quality CBD products, DOJ could make it clear that those products not meeting this research definition are Schedule I substances and will be subject to enforcement action. Currently, illegal purveyors of THC and CBD products are making rich profits off of Schedule I drugs, which they falsely promote to patients and other consumers as "legal dietary supplements," resulting in public health hazards.

DOJ and FDA should work together to take these products off the online "shelf."[1] It is encouraging that FDA recently stated that CBD products are not "dietary supplements." While the FDA has recently sent warning letters to some companies manufacturing CBD products illegally, FDA has traditionally resisted taking enforcement action in the area of medical marijuana, claiming that since marijuana (and its components, including THC and CBD) are Schedule I drugs, jurisdiction is left solely to DEA. However, several medical marijuana companies routinely and blatantly violate the Food, Drug and Cosmetic Act by selling foods and/or "medicines" that are dangerous, contain illegal

components, and have not been reviewed by FDA. Virtually none of these purveyors is complying with FDA requirements for proper manufacturing (GMP, registration with FDA), labeling and advertising/promotion. Manufacturers and other purveyors of marijuana products make many therapeutic claims that bring those products within the scope of the Food, Drug, and Cosmetic Act (FDCA).

Conclusion

CBD has the potential to help desperately ill individuals. At the same time, companies and individuals with little medical background are taking advantage of that fact. If we're prepared to remove CBD from the general issue of legalization – and out of the hands of activists with broader agendas - there are some practical things the federal government can do to both expand the experimental access of the product and set in place protocols to advance research and knowledge.