SB 844 Task Force Report: Researching the medical and public health properties of cannabis

Prepared on behalf of the Public Health Division,
Oregon Health Authority by

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Executive Summary

Senate Bill 844 created a Task Force instructed to assess the current state of cannabis research and to identify ways that the State of Oregon can address critical gaps in that research. Specifically, the Task Force was instructed to "study and make a report on the development of a medical cannabis industry that provides patients with medical products that meet individual patient needs."

The Task Force found that the existing body of research on cannabis lags severely behind most other fields of research, and that significant legal and regulatory hurdles still impede the completion of this research. The research necessary to support the development of an effective cannabis industry and to provide patients with effective medical products spans multiple scientific fields, and includes several different categories of study with varying regulatory restrictions. Some of this work can only be done effectively *within* universities, although in that setting it is severely restricted by federal cannabis laws. Other aspects of this research can only be effectively done *outside* of universities, although in that case it will be limited by federal guidelines on human subjects' research.

In order to support all of the different types of cannabis research that are necessary, the Task Force recommends the creation of an independent, free-standing Oregon Institute for Cannabis Research. This Institute would be empowered to conduct internal research and also to support external and collaborative research projects. It would require a sustainable source of funding from the state, but also be capable of raising funds from other sources. It would be overseen by a Scientific Advisory Board composed of internationally renowned researchers, and would be tasked with producing the most high-impact research possible, while adhering to rigorous scientific and ethical guidelines.

Such an Institute will be capable of driving forward critical research at a much faster pace than other similar attempts have been able to. It will have the broadest possible impact on the existing body of cannabis research, and will address questions that, in fact, cannot be addressed by any other means. This institute will position Oregon as a leader in cannabis research and serve as an international hub for what will soon be a rapidly accelerating scientific field. No other single initiative could do as much to strengthen the Oregon cannabis industry and to support the needs of Oregon medical marijuana patients.

Task Force Overview

Oregon residents have been able to access cannabis for medical use since 1998, when voters approved the Medical Marijuana Act, which established the Oregon Medical Marijuana Program (OMMP). That program currently has more than 77,000 medical cannabis patients registered.[1]

In 2014, the state expanded access to cannabis by becoming one of four states in the U.S. to allow recreational use of cannabis, joining Colorado, Washington, and Alaska. The state legislature also passed Senate Bill 844 in 2015 requiring the Oregon Health Authority to establish a task force to study the medical and public health properties of cannabis. Specifically, the task force was asked to address the following questions:

(a) Identify and assess the validity of research related to the medical properties of cannabis that have been conducted in other countries and in other states and territories of the United States;
(b) Assess the potential for this state to collaborate with other states that have legalized the medical or recreational use of cannabis for purposes related to researching the medical properties of cannabis;
(c) Identify key research areas related to the medical properties of cannabis;
(d) Identify legal barriers to the establishment of laboratories that research the medical properties of cannabis, including barriers related to the possession, delivery, and manufacture of marijuana;
(e) Identify legal barriers to the use of institutional review boards in approving, monitoring and reviewing research involving the medical properties of cannabis;
(f) Propose solutions to structuring and funding research that involves the medical properties of cannabis, including solutions that involve state programs and moneys and solutions that involve investment by private businesses and business sectors; and
(g) Assess the potential of locating a cannabis grow site for research purposes in this state and, if appropriate, setting forth a plan for the establishment of a cannabis grow site for research purposes in this state.

SB 844 designated 15 task force members representing specific areas of expertise. In December 2015, the Oregon Governor's office appointed the following members to the task force[1]:

Name	Expertise / Representing
Mowgli Holmes, PhD, (CHAIR)	Agricultural Research
Christopher Conrady	Oncology
Chris Edwards	Oregon State Senate
Peter Gendron	Marijuana Grow Site
Katrina Hedberg, MD, MPH	Oregon Health Authority
Robert Hitzemann, PhD	Oregon Health and Science University
Jane Ishmael, PhD	Oregon University System
Shannon O'Fallon, JD	Department of Justice
Jeremy Riggle, PhD	THC and CBD Measurement
Colin Roberts, MD	Neurology
David Russo, DO, MPH	Palliative Care
William Schuette	Oregon Liquor Control Commission
Anthony Smith, PhD	Microbiology
Daniel Sudakin, MD, MPH	Substance Abuse Treatment
Carl Wilson	Oregon House of Representatives

The Task Force met three times, on December 15, 2015, January 8, 2016 and January 26, 2016 to review current research related to the medical and public health properties of cannabis and other states' efforts to contribute to the body of cannabis research, and to develop recommendations to facilitate the establishment of a cannabis research program in Oregon.

Summary of Task Force Findings and Recommendations

The Task Force addressed the questions specified in SB 844, and came to the following conclusions:

(a) International and U.S. research related to the public health and clinical properties of cannabis is compelling and warrants a range of further research supported by the state.

[1] State employees representing the Oregon Health Authority, Oregon Liquor Control Commission and Oregon Department of Justice participated in this task force but the recommendations of the task force do not necessarily reflect the position of these agencies.

(b) Other states, most notably Colorado and California, are currently supporting federally sanctioned medical cannabis research programs, as are several other countries, including Israel, Uruguay, and Czechoslovakia. Opportunities to collaborate exist with several national and international research programs. In addition, Oregon should build upon these programs and support research not currently being conducted in other jurisdictions.
(c) There are many different critical areas of research related to medical marijuana, all of which need significant investment and development. These range from agricultural, genetic, and toxicological questions to pharmacological, epidemiological and clinical ones.
(d) Significant barriers exist to the establishment of laboratories that research the medical properties of cannabis, especially related to the possession, delivery, and manufacture of marijuana. However, these barriers have to do with the transport of marijuana for research across state lines and the use of marijuana for research within federally-funded universities. The state of Oregon cannot, at present, effectively address the first issue. It can address the second issue by taking steps to encourage and fund cannabis research outside of the university system.
(e) There are no legal barriers to the use of institutional review boards, nor do those boards limit useful research. However, for any non-university cannabis research institute to be effective, it will very likely have to find external and independent IRBs to review its studies, or provide for a centralized IRB with expertise in reviewing cannabis research.
(f) DEA restrictions on the cultivation of cannabis for research remain the most significant barrier to cannabis research. These can be addressed effectively by the state, but structuring and funding the necessary research will require institutional support that is external to the university system.
(g) Establishing a cannabis grow site for research purposes in Oregon is important and feasible. In order for a non-university research institute to be effective it will require the ability to grow and work directly with cannabis.

The Task Force recommended the following to move the field and industry forward and position Oregon as a national leader in cannabis research:

- The state should establish, and identify funding sources for, an independent Oregon Institute for Cannabis Research to conduct and support research relating to the medical and public health benefits of cannabis.
- State clinical licensing boards should clarify clinicians' expectations around recommending, prescribing, and discussing cannabis use for medical purposes, and conducting clinical research relating to cannabis.

I. State of Research on Medicinal Properties of Cannabis

Introduction to Medical Cannabis Research

Cannabis is one of the world's oldest known medicines,[2] with medicinal cannabis use dating back to 2727 B.C. in China.[3] By the 1850s, medicinal cannabis tinctures were patented in the United States and used for numerous ailments including cholera, rabies, dysentery, alcoholism, opiate addiction, insanity, and menstrual cramps, among others.[4] In 1963, the chemical structures of the main active compounds of the cannabis plant (i.e., cannabinoids) were identified,[5] sparking increasing interest in the pharmacological activity of cannabis. Since then, the number of publications analyzing the health effects of cannabis use increased dramatically throughout the 1970s.[6] However, with the passage of the Federal Controlled Substances Act of 1970, research on cannabis shifted to studies of the negative effects of cannabis use, including addiction. Interest in understanding therapeutic effects of cannabis was renewed again in the 1990s in part due to advancements in genetic cloning of specific receptors for cannabinoids in the nervous system.[6] Despite this interest, barriers to research have prevented the development of robust research programs evaluating the medical effects of cannabis.

Clinical research

The majority of the research involving cannabis has focused on its potential dangers and abuse liability. There are very few published papers on the biochemistry and genetics of the plant itself, and even fewer on its use as a therapeutic agent. Due to restrictive federal policies described below, only a limited number of randomized controlled trials, considered the "gold standard" of research, have evaluated the medicinal properties of cannabis. As with evaluating any other federally illicit substance, methodological challenges exist including ethical, legal, political, and practical barriers to such clinical trials.[7] True randomization is rare and ethical barriers limit cannabis dosage when controlled human experiments are possible. Other types of research methods such as animal models, pre-clinical trials, and observational studies do provide some information about the potential benefits of cannabis, but generalizability remains problematic. Animal experiments are restrictive, and generalizing health effects to human populations introduces uncertainty. Real world observational data present additional challenges because cannabis users and non-cannabis users differ in many immeasurable ways.[7]

Despite methodological limitations, a significant body of literature on the potential medicinal benefits of cannabis has developed, primarily from researchers outside of the U.S. (See Table 1). Table 1 summarizes clinical trials, animal models, observational studies, and pre-clinical trials assessing the medicinal properties of cannabis (See Appendix A for a detailed description of the therapeutic benefits of cannabis). Only 13 conditions listed in Table 1 have been studied using clinical trials, many with sample sizes of less than 100 participants. There is strong clinical support that cannabis use relieves many clinical conditions including nausea, chronic pain, and

spasms, and tics. As illustrated in Table 1, these conditions have the most clinical trials published with 30 or more studies conducted for each condition. There is intermediate evidence that medical cannabis use alleviates side effects of glaucoma, epilepsy, dementia, inflammation, and post-traumatic stress disorder (PTSD). Notwithstanding a plethora of published work on the therapeutic benefits of cannabis there remain significant research gaps for assessing the benefits of medicinal cannabis on diabetes, sleep, alcohol and substance use addiction, amyotrophic lateral sclerosis, leukemia, and Schizophrenia. The two Schizophrenia trials produced mixed results because one study administered CBD, which reduced schizophrenic symptoms, and the other administered THC, exacerbating symptoms. Neuroprotection, inflammation, BMI, and waist circumference research rely on animal models and observational studies with no clinical trials. Emerging studies include PTSD, pediatric epilepsy, and sleep trials (See Table 1).

Current State and Federal Cannabis Research Programs

In the U.S., the literature has been compelling enough for 23 states, the District of Columbia, and Puerto Rico to enact medical cannabis programs. Each state program specifies a list of conditions for which one may qualify to use medicinal cannabis. Appendix B provides state-specific qualifying conditions nationwide ranging from eight to 16 medical conditions and symptoms. The Oregon Medical Marijuana Program (OMMP) currently recognizes ten qualifying medical conditions including a degenerative or pervasive neurological condition, cachexia, cancer, glaucoma, HIV/AIDS, nausea, PTSD, severe pain, seizures, and persistent muscle spasms. Nearly 90% of Oregon's medical cannabis patients have one of three qualifying conditions: severe pain (74,432 cardholders), muscle spasms including those caused by Multiple sclerosis (22,587 cardholders), and nausea (10,975 cardholders).[8]

Table 1: Strength of Evidence for Clinical Conditions and Symptoms Treated by Cannabinoids

Clinical Condition Or Symptom	Articles[a]	Clinical Trial and Size	Country of Clinical Trial	Animal Trial[a]	Observational/ Pre-Clinical[a]
Nausea; Chemotherapy	Zuardi, 2008[6]; Rock, Limebeer, and Parker, 2014[9]; Amar, 2006[2]*; Grotenhermen, and Müller-Vahl, 2012[10]*	33 (N=8-172)	United States (17), The Netherlands (1), Scotland (1), Canada (3), Finland (2), Ireland (1), France (1), Great Britain (3), Germany (1), New Zealand (1), Switzerland (1), Spain (1)		
Chronic Pain	Martin-Sanchez *et al*., 2009[11]*; Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[12]*, Grotenhermen, and Müller-Vahl, 2012[10]*	32 (N=1-125)	United States (10), Belgium (2), Sweden (1), Switzerland (1), Great Britain (8), Germany (2), Canada (5), Austria (1), United Kingdom (2)		
Spasms and Tics; Multiple Sclerosis; Spinal Cord Injuries; Tourette's Syndrome	Lakhan and Rowland, 2009[13]*; Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[12]*; Grotenhermen, and Müller-Vahl, 2012[10]*	30 (N=1-630)	United States (6), The Netherlands (1), Denmark (2), Switzerland (2), Great Britain (12), Italy (3), Austria (1), Germany (2), Canada (1)		
Appetite Stimulation; Wasting Syndrome; Anorexia	Amar, 2006[2]*; Hazekamp and Grotenhermen, 2010[12]*; Grotenhermen, and Müller-Vahl, 2012[10]*	9 (N=12-469)	United States (8), Canada (1)		
Glaucoma	Jampel, 2010[14]; Amar, 2006[2]*	3 (N=8-18)	United States (2), Great Britain (1)		
Anxiety Disorders; Posttraumatic Stress Disorder	Greer, Grob, and Halberstadt, 2014[15]; Korem and Akirav, 2014[16]; Fraser, 2009[17]; Bonn-Miller, 2011[18]; Trezza and Campolongo, 2013[19]	3 (N=47-60)	United States (1), Canada (1), Germany (1)		
Intestinal Dysfunction	Hazekamp and Grotenhermen, 2010[12]*	2 (N=30-52)	United States (2)		
Schizophrenia	Hazekamp and Grotenhermen, 2010[12]*	2 (N=13-42)	United States (1), Germany (1)		

Clinical Condition Or Symptom	Articles[a]	Clinical Trial and Size	Country of Clinical Trial	Animal Trial[a]	Observational
Epilepsy	Amar, 2006[2]*; Porter and Jacobson, 2013[20]; Hill *et al.,* 2013[21]; Hill, Hill, and Whalley, 2013[22]*; Devinsky *et al.,* 2015[23]; Tzadok *et al.,* 2015[24]; Friedman and Devinsky, 2015[25]*	7 (N=1-162)	Brazil (1) United States (1) Israel (1)		
Hepatitis C	Hazekamp and Grotenhermen, 2010[12]*	1 (N=71)	United States (1)		
Sleep	CMCR, 2015[26];	1 (N=15)	United States (1)		
Diabetes	Rajavashisth *et al.*, 2012[27]; Muniyappa *et al.*, 2013[28]	1 (N=60)	United States (1)		
Cancer **Breast** **Prostate** **Lung** **Skin** **Pancreatic** **Bone** **Glioma** **Lymphoma** **Oral** **Head and Neck** **Thyroid**	Sarfaraz *et al.*, 2008[29]*; Alexander, Smith, and Rosengren, 2009[30]*; Chakravarti, Ravi, and Ganju, 2014[31]*	1 (N=177)[b]		>10 >10 <5 1 <5 >10 >10 <5 1 0 <5	1
Inflammation Rheumatoid Arthritis Inflammatory Bowel Diseases; Ulcerative colitis Crohn's Disease	Zuardi, 2008[6]* Esposito *et al.,* 2013[32]*; Blake *et al.*, 2005[33]	1 (N=58)	United Kingdom (1)	>10	
Addiction and Dependence	Reiman, 2009[34]; Hurd *et al.*, 2015[35]*	<5		>5	>5
Neuroprotection **Alzheimer's** **Amyotrophic Lateral Sclerosis (ALS)** **Parkinson Disease**	Russo and Guy, 2006[36]*; Carter and Rosen, 2001[37]	0		<5 <5 <5 <5	1
BMI and Waist Circumference	Rodondi *et al.*, 2006[38]; Penner *et al.*, 2013[39]; Le Strat and Le Foll, 2011[40]; Le Foll *et al.*, 2013[41]; Hayatbakhsh *et al.*, 2010[42]	0			>5

Notes: * Indicates a review article. a. No animal, observational, or pre-clinical trials were reported if a clinical condition or symptom was evaluated using clinical trials.
b. Randomized controlled trial on cancer pain.

State-Level Medical Cannabis Research Programs

Though many states have recognized the medicinal benefits of cannabis by enacting expansive medicinal cannabis programs, others have enacted limited access therapeutic research programs. Beginning in the 1980s, states began allowing access to cannabis for patients suffering from a more limited number of conditions, generally seizure disorders, and for whom other therapies were not effective. Though called "research" programs and requiring submission of some observational data to the state, these programs were intended to provide access to cannabis as a drug of last resort rather than to support evaluation of its effectiveness. According to the National Conference of State Legislatures, 16 states currently run these types of expanded access programs, several with explicit evaluative research expectations.[43] Table 2 lists the three states that are currently supporting broader research programs on the therapeutic properties of cannabis. Each of these programs is varied in its structure, funding, and type and focus of research supported. All programs require funded researchers to adhere to all current federal laws relating to cannabis supply and human subjects research.

Table 2: Comparison of California, Colorado, and Minnesota Clinical Research Programs

	California[a]	Colorado[b]	Minnesota
Administered by	University System	Colorado Department of Health	Minnesota Department of Health
Year Established	1999, 2003	May 2014	July 2015
Amount of Funding	$8.7 million	$9 million	
Source of Funding	State Funding*	State Funding*	Initially state funded, ongoing funding will come from manufactures' enrollment and from fees
Studies (raw number)	13	9	1
Types of Studies	Clinical trials	Observational and clinical trials	Observational only

Notes: *Authorized to accept private donations. a. Completed studies. b. Approved studies.

***California*.** In 1999, California legislature passed Senate Bill 847, establishing the University of California Center for Medicinal Cannabis Research (CMCR).[44] CMCR, established in 2000, is housed within the University of California, San Diego and conducts clinical and pre-clinical trials researching the therapeutic value of cannabis.[26] The institute is the sole recipient of funding from the state of California for medicinal cannabis research. Areas of emphasis for the Center's 13 research studies were: severe appetite suppression and weight loss due to HIV, chronic pain (particularly neuropathic pain), severe nausea associated with cancer, and severe muscle

spasticity. CMCR's legislative report concludes that "they have reasonable evidence" that cannabis is a promising treatment for pain caused by nervous system disorders and painful muscle spasticity due to multiple sclerosis.[44]

***Colorado*.** Colorado established the Medical Marijuana Research Grant Program in May 2014.[45] The program is supported by Colorado's Medical Marijuana Scientific Advisory Council and the Board of Health and administered by the state health department. In 2015, the council approved nine research grants using a surplus of nine million dollars in medical cannabis tax revenue (See Table 2). Similar to California, the state of Colorado issued calls for applications from researchers. Areas of research emphasis include PTSD, pediatric epilepsy, and pediatric brain tumors, among others. All nine studies are in the beginning stages of research. Both California and Colorado require individual researchers to obtain necessary federal and state approvals to conduct their proposed research.

***Minnesota*.** Minnesota has one of the United States' most limiting medical cannabis policies in that medical patients are permitted to use a liquid or vaporized form of cannabis but not smoked cannabis or edible cannabis products. In contrast to the Colorado and California program which recruited participants for clinical studies, Minnesota researchers survey every medical cannabis patient in the state registry, 662 patients to-date, as part of one ongoing observational study.[46]

***Expanded Access Research Programs*.** Several states established new therapeutic cannabis research programs in 2014-2015 that authorized clinical and/or observational studies. In comparison to California and Colorado, which allowed researchers to submit abstracts, these states specified a limited number of specific conditions (mainly pediatric seizures) and a specific cannabis product to evaluate potential benefits of cannabis and its derivatives. (See Table 3 for a list of cannabis-based pharmaceuticals.)

- Georgia has authorized an expanded access study through the University of Georgia system [47] and in partnership with GW Pharmaceuticals which is administering the study in several states. The study utilizes a pharmaceutical grade cannabis derivative, Epidiolex, already FDA approved for treatment of Dravet Syndrome. The study has cost an initial $4.8 million in state funding and is receiving Epidiolex free of charge from the manufacturer.
- The Alabama Legislature passed Carly's Law in 2014[48] approving a $1 million expanded access study. Similar to Georgia, this study is receiving a pharmaceutical cannabis derivative from GW Pharmaceuticals at no charge.
- North Carolina similarly permits the use of hemp extract for treatment of "intractable" epilepsy.[49] North Carolina's Department of Health and Human Services is now authorized to

approve pilot studies evaluating the effectiveness of hemp extract for epilepsy, although there is no indication that trials have begun.

Table 3: Cannabis and Cannabis Based Pharmaceuticals

Substance	Schedule Designation	Notes
Medical Cannabis (whole plant) • THC delta-9-tetrahydrocannabinol • **CBD cannabidiol**	Schedule I	Federally legal supplies (DEA Approved) only available through NIDA.
Artisanal Cannabidiol (CBD) purified oil or liquid	Schedule I	
Industrial Hemp extract	Schedule I but with exceptions	2014 Agricultural Act allows colleges and state agencies to grow and conduct research on hemp if otherwise legal under state law. (Legal in Oregon)
Epidiolex (Pharmaceutical Grade CBD)		Phase III clinical trials with possible approval in 2016
Cesamet (synthetic Nabilone)	Schedule II	FDA approved for nausea and vomitir with chemotherapy
Marinol® (synthetic Dronabinol)	Schedule III	FDA approved for weight loss due to AIDS/Anorexia
Sativex®		United Kingdom approved. Received FDA "Fast Track Designation" in 2014
Cannador®		Germany Not FDA approved
Veregen®		FDA approved botanical drug for venereal warts, topical green tea
Fulyzaq®		FDA approved botanical drug for treatment of diarrhea in HIV/AIDS

Current Federal Government Funded Studies

As of January 31, 2014, the federal government through NIH also had funded 30 studies addressing the therapeutic use of cannabis for six categories of medical conditions including seizures, substance use disorders, psychiatric disorders, autoimmune diseases, inflammation, and pain (See Appendix C).[50]

II. Legal Requirements for Cannabis Research

As indicated by the summary of research above, human subjects' research on the medicinal properties of cannabis is permitted in the United States. However, it is strictly controlled by federal agencies. Pursuant to the Convention on Narcotic Drugs, the U.S. must designate a federal level agency to control production and distribution of cannabis and other narcotic

drugs. The U.S. Drug Enforcement Agency (DEA) is the responsible agency for the U.S. and as part of its responsibilities, categorizes drugs by their relative level of abuse potential. The DEA continues to place cannabis on Schedule I, which includes drugs with "high abuse potential" and "no accepted medical use."[51] With that designation, the production, transportation, or possession of cannabis not explicitly approved by the DEA is illegal under federal law. The Controlled Substance Act (CSA) also includes explicit requirements relating to research with Schedule I substances. Researchers wishing to conduct research using a Schedule I substance must first register with the DEA, which must determine the qualifications and competency of the researchers as well as the merits of the research protocol[52].

Despite the CSA's general prohibition of cannabis, the U.S. Department of Justice (DOJ), is not prosecuting production, dissemination, or possession of cannabis that has been legalized for medical or recreational use under state laws. In 2009 and 2013, the DOJ issued a series of memoranda that indicated it would defer to state and local enforcement of medicinal cannabis as long as the states implemented "strong and effective regulatory and enforcement systems."[53] The Memorandum identify the agencies enforcement concerns focused on 8 areas:

1. Preventing the distribution of marijuana to minors;
2. Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels;
3. Preventing the diversion of marijuana from states where it is legal under state law in some form to other states;
4. Preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking or other illegal drugs or other illegal activity;
5. Preventing violence and the use of firearms in the cultivation and distribution of marijuana;
6. Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use;
7. Preventing growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands; and
8. Preventing marijuana possession or use on federal property.

These memoranda articulate enforcement priorities and how the DOJ's prosecutorial discretion will be utilized and have provided adequate assurances for some states to enable both medical and recreational marijuana use. In December 2015, Congress also approved language in the 2016 Consolidated Appropriations Act that prohibits the Department of Justice from using its federal funds to interfere with state medical cannabis programs.[54] However, the memoranda and instructions for 2016 federal monies do not change or nullify existing federal laws relating to cannabis. Cannabis remains illegal for any non-federally approved use at the federal level. Furthermore, entities that receive significant federal funding, such as universities and hospitals

(which receive monies from NIH or the Medicare Program), agree as a condition to that funding, to comply with federal laws. The Drug Free Schools and Communities Act also places explicit requirements on institutions of higher education to follow federal drug policy laws.[55] With respect to cannabis, using a non-federal government sanctioned (DEA approved) cannabis supply remains illegal under federal law and could therefore jeopardize federal funding.

Clinical Research: Cannabis Research Using Human Subjects

Food and Drug Administration New Drug Approval Process

In addition to the control of certain substances through the Controlled Substances Act, the Federal Food, Drug, and Cosmetic Act (FDCA) and National Research Act govern the conduct of drug research involving human subjects and controlled substances. Those laws contain provisions that allow for clinical (human subjects) research with investigational drugs, including Schedule I substances, provided certain steps are taken to protect the rights, safety, and welfare of human subjects. The FDA is responsible for reviewing the safety and efficacy of drug products. The agency requires drug manufactures to submit to a multi-step approval process designed to demonstrate that the drug is safe and effective for its intended clinical use (prescription or over the counter). The process includes both pre-clinical (investigational new drug – IND) and clinical (new drug application – NDA) reviews of the product. The agency is also responsible for ensuring that drug products are manufactured according to good manufacturing processes that ensure the quality and consistency of the product. The standards of evidence differ somewhat for synthetic or highly purified drugs compared to botanical drug products. The FDA has indicated it would review cannabis under its botanicals process though highly purified or synthetic components (such as CBD) would be subject to the agencies standard drug approval process. These botanical drug specific guidelines recognize the complex nature of botanicals and require researchers to submit documentation of the identity, quality, strength, potency, and consistency of the botanical (rather than an identification of the active ingredients as required for synthetic or highly purified drugs), although only one such botanical drug has ever been approved via this pathway. (See Appendix D).

Institutional Review Boards Requirements

Most research involving human subjects must be approved by federally regulated Institutional Review Boards (IRBs) charged with insuring that human subjects are not subject to unreasonable risk as a result of their participation in trials. Federal IRB requirements apply to "all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency."[56] This includes all research funded by the federal government and research intended to support applications for research or marketing of products regulated by FDA. IRBs are registered with the federal government and those

reviewing research involving potential drug products operate under Department of Health and Human Services regulations as well as FDA IRB regulations.

Though IRBs do not constitute a legal barrier to cannabis research, in practice, IRB reviews of research protocols involving cannabis and particularly studies involving children are rigorous. As long as cannabis is characterized as a Schedule I drug at the federal level, IRBs should treat it as such and the risks of administration of a drug with high abuse potential must be adequately mitigated in the study design/protocols. Furthermore, the protocols should ensure secure storage, handling, and disposal of cannabis products. The existing federally supported trials have developed protocols that adequately ensure both the safe storage and transfer as well as safe and proper administration of cannabis in studies, however many researchers have described the process of obtaining IRB approval for studies as lengthy and arduous.

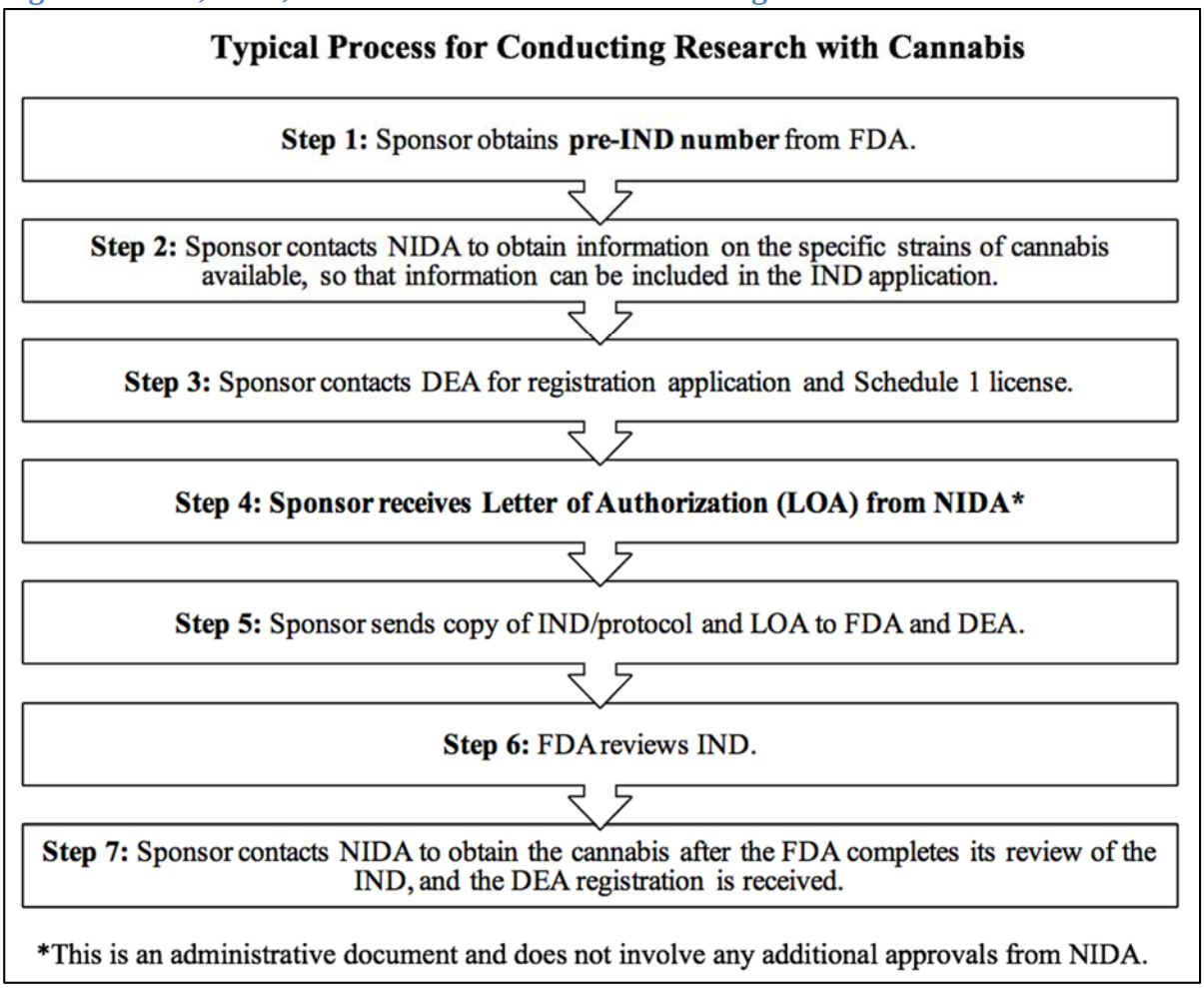
Procuring Cannabis for Clinical Research

Currently, cannabis and its components may be utilized in research if the research has been approved by three federal agencies.[57] Individuals wanting to conduct clinical research with cannabis must:

1) Apply to the U.S. Food and Drug Administration (FDA) for investigational new drug application approval (FDA applications also require that research protocols be approved by Institutional Review Boards)
2) Obtain a DEA certificate to handle and conduct research on Schedule I substances, and
3) Apply to the National Institute on Drug Abuse (NIDA) to receive the federally approved research grade cannabis[58] (See Figure 1 below).

In practice, the enforcement of these requirements has created barriers and delays for researchers, particularly those working through the process for the first time.

Figure 1: FDA, DEA, and NIDA Process for Conducting Research With Cannabis



NIDA Drug Supply Program

Pursuant to the CSA, the DEA remains responsible for the control and supervision of cannabis supplies for research. The DEA thus far has only issued one license to supply clinical research grade medical cannabis, NIDA (U.S. Patent #6630507 held by USA under DHHS). NIDA reviews all request for research grade cannabis and currently contracts with the University of Mississippi to manufacture cannabis products for research. That supply is available to researchers, however obtaining cannabis supply has been problematic in practice. NIDA has only approved supply for 16 non-federally funded studies since it began overseeing cannabis production in 1974.[59] Even those researchers who were able to obtain supply indicated that they have experienced significant delays in the process. The supply grown at NIDA is limited.[60] Additionally, some researchers note that the supply does not include varieties currently available in state marketplaces. Anecdotally, researchers with current studies indicate that they have found NIDA responsive to their needs and willing to produce products meeting the needs of research programs. That can, however, be a lengthy process.

The NIDA approval process includes several factors that influence the researcher's ability to obtain cannabis. First, NIDA does prioritize federally funded research. NIH funded studies are first to receive cannabis supplies from NIDA and much of the NIDA supply services addiction/abuse related studies that serve NIDA's own mission.[61] Second, though there is no explicit preference for closed system research programs (where funding and research institutions are the same organization, like the California program), such systems have been more successful in obtaining supply from NIDA than programs where the funding entity and the researcher are not part of the same entity (i.e. Colorado).

If the state wished to produce cannabis products for research, Oregon can also apply to the DEA be the legal supplier of cannabis for NIDA, though the distribution would still be managed by NIDA. NIDA regularly solicits proposals for organizations to produce the NIDA supply of research grade cannabis. The University of Mississippi has held that contract since 1968, most recently winning the competitive bid again in the summer of 2015.[62] Mississippi's current contract runs through 2016 with up to four additional yearlong extensions. University of Massachusetts researchers also attempted to receive approval for a research growing facility from the DEA in the 2000's but were denied even after engaging in a lengthy appeals process and legal battle.[63] The state also could request a separate license from the DEA, though the DEA has not indicated its willingness to approve additional research cannabis grow sites.

Non Clinical Research (Public health/Observational)

Researchers may also conduct research without directly supplying cannabis to enrolled subjects. These types of observational studies may be subject to varying legal requirements. Federally funded research or research being conducted by hospitals or universities will still require IRB approval. However, privately funded research conducted outside of universities and hospitals that intends to contribute generalizable knowledge but not FDA regulated (i.e. part of an IND or IND application) research may not require federally regulated IRB review.[64] The federal IRB regulations, referred to as "the Common Rule" are currently undergoing significant revisions. One of the proposed changes to the Common Rule would remove the discretion of IRBs to apply different sets of standards to federally funded (or federally IRB review required) studies and non-federally funded studies.

Plant Research

Under the CSA, manufacturers or laboratories wishing to grow or analyze cannabis must receive approval from the DEA to do so. Thus far the DEA has not demonstrated an interest in increasing the number of labs authorized to conduct research on cannabis. Cannabis supplies are also available for analysis through NIDA. NIDA may provide supplies to non-NIH funded, non human subjects research protocols if the scientist can demonstrate both their expertise and the scientific validity and ethical soundness of the research protocol.[65]

Hemp

The 2014 Farm Bill removed industrial hemp from some Schedule I restrictions by allowing states and universities in states where hemp has been legalized, (such as Oregon) to grow hemp crops for agricultural research.[66] Since the farm bill was enacted, at least 14 states have authorized hemp research and the Kentucky Department of Agriculture has established a state Department of Agriculture hemp growing and research program. State organizations wishing to grow hemp may do so without a DEA Schedule I manufacturer licensure. However, they may only import foreign hemp seed if licensed as an importer by the DEA. Additionally, in its communications with Kentucky, the DEA also has indicated that the state may distribute hemp seeds to state universities/researchers, as well as private farmers as long private entities also agree to comply with all federal laws.[67] (In Oregon, at least Oregon State University has recently taken steps to establish a hemp research program.)

The Evolving Federal Landscape

In recognition of increasing interest in research regarding the medicinal benefits of cannabis and its components, some federal agencies have revisited some of the details of those restrictions detailed above over the last two years, simplifying the processes and increasing the availability of cannabis supply.

- The Department of Health and Human Services recently revised the guidelines, first published in 1999, regarding the provision of cannabis for medical research through NIDA. In the revision, the FDA eliminated the need for a fourth agency – the Public Health Service – approval for research but retained the requirement that supply come from NIDA.[68]
- FDA staff have verbally expressed that it would consider applications involving non NIDA produced cannabis products but notes that the University of Mississippi farm has completed all filings for the FDA's Master Drug File. That means that the farm has submitted detailed information on the manufacturing facilities, processes, and materials. Though completion of the Master Drug File process is not required of manufacturers,[69] the FDA indicated that it would expect alternative cannabis manufacturers/growers to complete the process.
- NIDA itself and the National Institute of Health are funding research on the therapeutic benefits of cannabis.[70] NIDA also announced in May 2014 that it would significantly increase the supply of clinical research grade cannabis from 21 Kgs per year to 650 Kgs.[71] In June 2015 testimony to congress, NIDA Director Dr. Nora Volkow supported the need for clinical studies of CBD and identified the current research barriers, including the lack of CBD that has been produced under the guidance of Current Good Manufacturing Processes (cGMP) (required for testing in human clinical trials) as well as the variable quality and purity of CBD from state medical marijuana program sources.[72] (Note: Dr. Volkow also provided significant testimony to congress on the adverse health effects of cannabis a year earlier.)

- Following inquires from members of congress, DEA Deputy Assistant Administrator Joesph T. Rannazzisi testified that the "DOJ and DEA are fully committed to supporting lawful research involving marijuana and CBD by ensuring compliance with the Controlled Substances Act and the Single Convention on Narcotic Drugs. DEA will continue to review the relevant regulations to ensure they are consistent with supporting lawful research. If this review determines that amending the existing regulations governing the Schedule I researcher registration process is necessary to accomplish these goals, DEA would initiate the process to do so.[73] He also indicated a significant increase in approved cannabis researchers. As of June 4, 2015, there were 265 active researchers registered with DEA to conduct bona fide research with marijuana and marijuana extracts that include CBD, and 41 (up from 16 in November 2014) researchers approved to conduct research with CBD on human subjects…. In furtherance of our ongoing efforts to support CBD research, DEA will continue its policy of expediting these applications."[70]

Despite increasing support from DHHS and encouraging testimony, the FDA re-iterated that the DEA is the lead agency and the FDA will continue to follow its classification of cannabis as a Schedule I substance. Further, the FDA "will continue to play its role in ensuring that any new therapies (including those derived from cannabis) are safe, effective, and manufactured to a high quality, applying the drug development paradigm that continues to provide new medicine that meet these standards for patients."[74] Though the DEA, in compliance with the Obama administration's position, has thus far indicated that it will not interfere with state initiatives and though it has approved significant researchers to work in the area, it has not demonstrated willingness to allow other sources cannabis beyond the NIDA controlled supply. DEA official policy statement documents still posted on the agencies website are also strongly worded and indicate that the DEA continues to find that cannabis possesses no legitimate medical uses.[75] Indeed, DEA leadership has been widely criticized for its overly strong statements on the issue – referring to medical cannabis as a "joke."[76] The DEA's restrictions on the manufacturing and delivery and possession of cannabis, combined with requirements that Universities and other institutions receiving federal funds comply with federal cannabis laws, remain the most significant barrier to clinical and plant based research.

III. Findings and Recommendations of the Task Force

Findings/ Recommendations

Recommendation #1: Creation of the Oregon Institute for Cannabis Research.

The task force recommends Oregon create an "Oregon Institute for Cannabis Research" (Institute). ***The Institute's Mission shall be to conduct and support high-impact scientific research on the medical, biological, industrial, and public health properties of cannabis***.

A) Structure. The Institute should be a free-standing research organization that is enabled to perform the duties listed in subsection C below. It should be structured as a quasi-independent entity (such as a public corporation or a state-supported non-profit) able to accept funding from both the state and other sources. It will require internal scientific and research capabilities, at least 2-3 internal Principal Investigators, and administrative support for both internal and external research projects.

B) Governance. The Institute shall be guided in its mission by a governing board appointed by the Oregon State Governor, and by an Executive Director chosen by the board. This internal board will oversee all non-scientific institute activities and liaison with the legislature, relevant state agencies and the governor's office. An external scientific advisory board (SAB) comprised of individuals identified by the governing board and reflecting the institute's research interests, would be responsible for reviewing all applications for funding and providing ethics oversight for the institute.

C) Specific Duties of the Institute shall include:

1. Conduct research, and support research by other public and private entities, relating to the medical, biological, agriculture, and public health properties of cannabis. The Institute shall not limit its research activities or support to a particular area of cannabis research but rather strive to support a range of research activities, including:
    - Basic plant and agricultural research. For medical cannabis research to be successful, the cannabis plant must be studied in parallel to fully understand the properties of the plant.
    - Public health research. With both medical and adult-use (recreational) cannabis available in Oregon, research on the public health impacts of cannabis use is needed. Research projects designed to assess impacts of policies (such as those relating to time, place and manner of sale) on use, attitudes, and health effects would provide important information for developing policies and procedures for cannabis retail and medical distribution systems, as well as to inform interventions to mitigate potential negative impacts of cannabis legalization. Many public health questions around

cannabis also involve toxicology and contamination issues that can only be resolved by working with directly with cannabis grown in Oregon.

- Observational Studies related to the medical benefits of cannabis. Though observational studies alone will not lead to FDA approval or medical use more broadly accepted by the medical community, observational studies are useful in providing evidence of the likely medical and public health benefits of cannabis and in supporting the development of clinical research studies.
- Pre-Clinical research. Research establishing the safety and efficacy of cannabis and its components is necessary to obtain FDA approval to conduct clinical (human) research.
- Clinical research (meeting FDA standards). Rigorous clinical trials meeting FDA standards are necessary to develop the evidence base for use of cannabis use in Oregon and lead to products FDA approved for medical use.

2. The Institute shall divide its funding support between federally approved university-based research that cannot be done outside of universities, and research done internally or collaboratively that cannot be done effectively within universities.
3. The Institute shall solicit proposals to conduct cannabis research from public and private entities, as well as from internal researchers within the Institute. It will evaluate those requests for funding, and determine funding for those projects from available resources.
4. The Scientific Advisory Board shall use a rigorous peer review process to select research grant applications for funding. This process will be designed to maximize the Institute's support for research that will be of the highest possible impact in the scientific community; that will answer critical questions necessary to promote the health and safety of Oregonians; and that will support the sustainable growth of the Oregon cannabis industry. Additionally, the peer review process will be designed to guard against funding research that is biased in favor of or against particular outcomes, or that brings up potential conflicts of interest. The Scientific Advisory Board will be responsible for the peer review process, and will be empowered to contract with external reviewers, when necessary, who shall be selected for their expertise in the scientific substance and methods of the proposed research and their lack of bias or conflict of interest regarding the applicants or the topic of an approach taken in the proposed research.
5. The Institute shall be empowered to develop partnerships, collaborations, or contractual relationships with public and/or private entities within the U.S. and other countries in furtherance of the Institute's objectives
6. The Institute shall receive funds allocated by the state to support cannabis research. The Institute also shall apply for and accept funds from foundations, private

individuals, and other sources as long as such funds do not compromise the objectivity of the research in any way.

7. The Institute shall monitor cannabis research conducted by or supported by the Institute, insuring that all research remain free of financial or other conflicts of interest and that all research involving human subjects meet institutional review board (IRB) requirements. The Institute may contract with external or independent IRBs as necessary, or even explore the possibility of creating an internal IRB.
8. The Institute should develop and maintain a centralized, secure, web-based research participant registry for citizens who want to learn about getting involved in IRB-approved research studies involving medical cannabis. For example, OMMP applications could include a box to check if patients are interested in becoming involved.
9. The Institute should develop and maintain resources to assist researchers conducting cannabis research. This should include the creation of partnerships and data-sharing arrangements with other institutions and relevant state agencies in order to assemble, organize, and make available as much collected data as possible on the use of cannabis in the state of Oregon.
10. The Institute shall provide administrative and structural support for university-based researchers in Oregon working on cannabis-related issues (whether or not they have received Institute funding) in order to expedite the process of obtaining federal approvals for research.
11. The Institute shall identify policy and other barriers to cannabis research, make appropriate recommendations to state agencies in addressing those barriers, and strive to find internal or collaborative routes toward completing research that is hindered by such barriers.
12. The Institute shall be capable of growing, handling, and studying the Cannabis plant itself, just as any other OLCC Marijuana Program Licensee is, and shall operate under a specific OLCC license (either the existing Research Certificate or another custom license type if that is deemed more appropriate). The Institute shall be empowered to grow cannabis on-site, and to create additional satellite growing locations through contract, collaboration, or new license applications as necessary.

D) Funding. To enable the Institute to meet these objectives, the Task Force recommends the state allocate sufficient funds both to support the development of Institute infrastructure and to serve as a sustainable source of research funding. No other states have provided *sustainable* funding for cannabis research; doing so would establish Oregon as a leader in this field immediately. The most feasible source of such funding would be a re-allocation of the tax revenue from the Oregon recreational cannabis

program itself. Because of the many ways that an Oregon state cannabis research institute would strengthen and support the Oregon cannabis industry, such a use of these revenues will be the best way to ensure the continued stability and growth of this entire revenue source in the future.

E) Data access. Additionally, the Task Force recommends that the legislature direct state agencies, including but not limited to OHA, ODA, and OLCC to share relevant data, when possible, for Institute-approved research studies.

Recommendation #2: Clarifying expectations for licensed medical professionals

The Task Force also identified several additional barriers in the state to physician participation in cannabis research. Therefore, task force members recommend that clinical licensing boards such as the medical, pharmacy and nursing boards clarify expectations for health care professionals engaged, or those planning to engage, in clinical cannabis research. Specifically, the Task Force recommends that the state:

a. Request the Oregon licensing boards clarify their position (develop a statement of philosophy) on licensee's conducting well regulated cannabis research (i.e. would such participation be considered negligence or a violation of their practice acts?).
b. Request the Oregon licensing boards clarify their position on licensee's recommending and discussing cannabis products (i.e. would such participation be considered negligence or a violation of their practice acts?).
c. Recommend ongoing education and training regarding state cannabis laws for practitioners affected by these laws.

Appendix A: Clinical Conditions and Symptoms Treated by Cannabinoids

Nausea and Appetite Stimulation

Cannabis is used to alleviate the treatment side effects of two leading causes of death globally, cancer and HIV. One of the first therapeutic uses of cannabis in an evaluated clinical trial successfully treated patients' nausea and vomiting induced by cancer chemotherapy. Results from studies using rat and mice models also support claims that cannabis suppresses nausea in patients undergoing chemotherapy.[6] Similarly, smoking or ingesting cannabis is used by patients experiencing AIDS-related wasting syndrome and anorexia. Longitudinal cohort studies report patients using cannabis to alleviate antiretroviral therapy (ART) side effects by stimulating their appetite leading to weight gain and improving their mood and quality of life.

Chronic Pain

Cannabis has been used to treat chronic pain for centuries in traditional medicine A meta-analysis of eighteen clinical trials suggests that cannabis is moderately efficacious for treating chronic pain.[11] Neuropathic pain–a chronic pain state caused by chemotherapy, diabetes, HIV, Multiple sclerosis, amputation, alcoholism, shingles, or spinal cord injuries, among other causes–is also alleviated with cannabis.

Inflammation

Rheumatoid arthritis is an autoimmune disease associated with chronic inflammation. Cannabinoids have anti-inflammatory properties due to a combination of immunosuppressive and anti-inflammatory responses.[6] Animal models have shown promise that cannabis is an effective treatment for rheumatoid arthritis[6] and inflammatory bowel diseases, namely ulcerative colitis and Crohn's disease.

Glaucoma

Glaucoma is a disease of the optic nerve caused by increased levels of intraocular pressure. Cannabis has definitively demonstrated a reduction in intraocular pressure in the general population and glaucoma patients who use cannabis.[14] Patients smoke cannabis, ingest pills containing the active ingredient in cannabis, or use eye drops with tetrahydrocannabinol to reduce and slow the progression of optic nerve damage. However, due to cannabis' short period of relief, cannabis would have to be ingested every few hours every day for the patient's life, and thus, the American Glaucoma Society does not support cannabis to treat glaucoma.[14]

Epilepsy

Possibly the most publicized therapeutic treatment of cannabis is for children with epileptic seizures. The media has followed many stories of children whose families moved to states with legalized medical cannabis in order to reduce their children's seizures out of desperation. Many of these children were having up to 200 seizures per day with no prior effective treatment. According to parental surveys, the seizures slowed and reduced in number after using special strains of cannabis that contain high levels of cannabidiol (the primary non psychoactive constituent of the cannabis plant) and low levels of tetrahydrocannabinol (the primary psychoactive part of the plant).[20] In addition to the anecdotal stories and surveys, there is also support of cannabis as an effective treatment of epileptic seizures using animal models.[21] Colorado is in the process of beginning two observational studies reviewing the effect of cannabis on pediatric epilepsy.

Spasms and Tics

Spasticity–one of the most common side effects of Multiple sclerosis–is an involuntary muscle spasm alleviated by using a cannabinoid mouth spray. A review article evaluated six randomized human studies and noted a reduction in spasms of patients with multiple sclerosis following the use of cannabis. Studies on the

effectiveness of cannabis and Tourette's syndrome produced similar results. Two German controlled trials observed significant decreases in tics after Tourette's patients received oral tetrahydrocannabinol.

Tumor Reduction

Cancer is a disease characterized by the division and multiplication of cells with damaged DNA. Mechanisms that interrupt the signaling involved in cell proliferation are needed for the management of cancer. Although there is some contradictory evidence of the effectiveness of cannabis on cancer growth, cannabinoids have been shown to inhibit tumor cell growth and prolong life since the early 1970s.[29] Three recent review articles demonstrate the anti-proliferative action of cannabinoids in brain, prostate, breast, lung, skin, pancreatic, uterine, thyroid, and lymphoma cancer cells.[29] [31] [30]

Neuroprotection

Humans have two types of cannabis receptors in their body, CB_1 and CB_2. The preceding section described the ability of cannabinoids to bind to these receptors discouraging cancer cell proliferation. The same binding occurs for patients with Alzheimer's disease slowing the progression Alzheimer's and reducing neuroinflammation. The neuroprotective roles of cannabidiol and tetrahydrocannabinol are effective treatment for migraines, anxiety, Alzheimer's, amyotrophic lateral sclerosis (ALS), Parkinson disease, and Multiple sclerosis.[36]

Anxiety Disorders

A current hot topic in the popular media is the therapeutic potential of cannabis to relieve anxiety for people suffering with post-traumatic stress disorder (PTSD). New studies have led some scientists to recommend cannabis as a treatment of PTSD symptoms in veterans. In 2014, two studies described the reduction of PTSD symptoms using surveys[15] and in vivo utilizing synthetic cannabis.[16] Two studies are underway in Colorado examining the effects of medicinal cannabis on PTSD.

Additional Benefits

Additional health benefits of cannabis use include lowering the risk of diabetes in cannabis users compared to non-users,[27] maintaining smaller waist circumferences and lowering BMI in cannabis users compared to non-users,[39] and helping those suffering from other forms of addiction such as alcoholism and opiate addiction.[34] These therapeutic benefits lack the epidemiologic and scientific evidence than those presented above. Further studies are warranted to substantiate the pilot studies' therapeutic claims.

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Appendix B: State Specific Qualifying Medical Conditions for Medical Cannabis Cardholders[77]

States	AK	AR	CA	CO	CT	DE	DC	HI	IL	ME	MD	MA
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glaucoma	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓
AIDS/HIV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Crohn's Disease		✓	✓		✓				✓	✓		✓
Hepatitis C		✓	✓						✓	✓		✓
Multiple Sclerosis			✓		✓				✓			✓
Amyotrophic Lateral Sclerosis		✓	✓			✓	✓		✓	✓		✓
Post Traumatic Stress Disorder			✓		✓	✓				✓		✓
Cachexia, Anorexia, or Wasting Away Syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Severe or Chronic Pain	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓
Severe or Chronic Nausea	✓	✓	✓	✓		✓		✓		✓	✓	✓
Seizure Disorders	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓
Muscle Spasticity Disorders	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Agitation of Alzheimer's		✓	✓			✓			✓	✓		✓
Other (arthritis, Parkinson's, hospice)			✓		✓	✓	✓		✓			✓
Allows Addition of Diseases or Conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

States	MI	MN	MT	NV	NH	NJ	NM	NY	OR	RI	VT	WA[78]
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glaucoma	✓		✓	✓	✓	✓	✓		✓	✓		
AIDS/HIV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Crohn's Disease	✓	✓	✓		✓	✓	✓	✓				
Hepatitis C	✓				✓		✓			✓		
Multiple Sclerosis			✓		✓	✓	✓	✓			✓	✓
Amyotrophic Lateral Sclerosis	✓	✓			✓	✓	✓	✓				
Post Traumatic Stress Disorder	✓			✓			✓		✓			
Cachexia, Anorexia, or Wasting Away Syndrome	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Severe or Chronic Pain	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Severe or Chronic Nausea	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Seizure Disorders	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Muscle Spasticity Disorders	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓
Agitation of Alzheimer's	✓				✓				✓	✓		
Other (arthritis, Parkinson's, hospice)		✓	✓		✓			✓				
Allows Addition of Diseases or Conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓

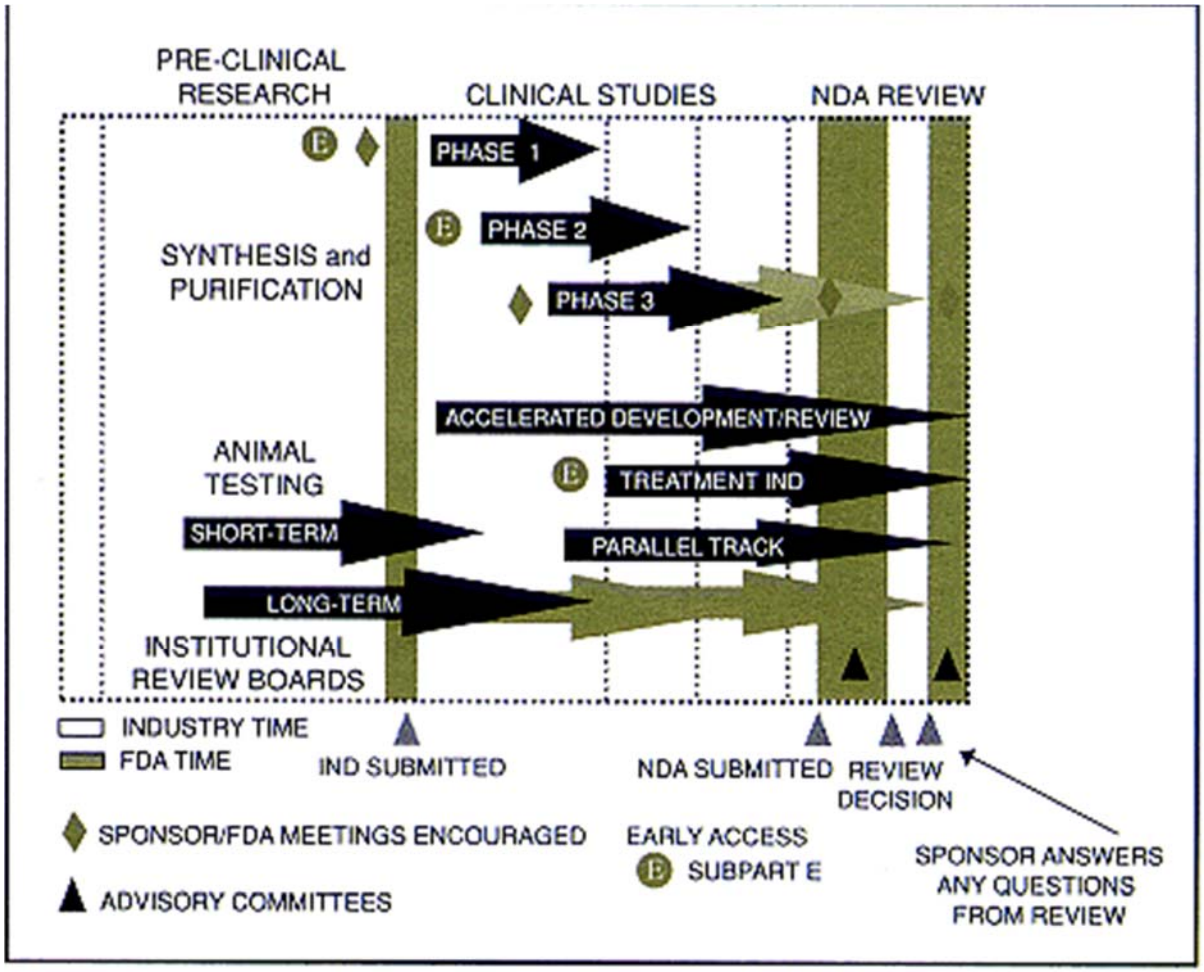
Appendix C. National Institute of Health Sponsored Studies since January 31, 2014

Project Title	Cannabinoid	Study Model
Seizures		
New Drugs to Enhance Endocannabinoid Responses for **Treating Excitotoxicity, Phase**	Endogenous (AE via FAAH inhibitors)	Animal
SUD, Withdrawal, and Dependence		
Cannabinergic Medications for Methamphetamine Addiction	Synthetic (CB1 agonists and antagonists, proprietary)	Animal
Efficacy and Safety of Dronabinol (Oral THC) for treating Cannabis Dependence	Synthetic (Dronabinol)	Human
Evaluation of Novel Pharmacotherapies for the treatment of Opioid Dependence	Synthetic (Dronabinol, Nabilone)	Human
FAAH- Inhibitor for Cannabis Dependence	Endogenous (AE via PF-04457845 FAAH inhibitor)	Human
Marijuana Relapse: Influence of Tobacco Cessation and Varenicline	Sythetic (Dronabinol)+/- the noncannabinoid varenicline	Human
Medications Development for Cannabis-Use Disorders: Clinical Studies	Purified (THC) and non-cannabinoids: Gabapentin & Tiagabine	Human
Monoacylglycerol Lipase Inhibitors for treating Opioid Use Disorders and Supplement	Endogenous (2-AG via JZL184 MAGL inhibitor)	Animal
Nabilone For Cannabis Dependence: Imaging and Neuropsychological Performance and Supplement	Synthetic (Nabilone)	Human
Novel Medications Approaches for Substance Abuse	Synthetic (Dronabinol, Project4)+noncannabinoid lofexidine	Human
Novel Medications for Cannabis Dependence	Synthetic (Modify THC and nabilone to create new cannabinoids)	Animal
Sativex Associated with Behavioral Prevention Relapse Strategy as Treatment for and Supplement	Purified (Sativex) +/- behavioral therapy	Human
Stress-Induced Marijuana Self-Administration: role of Sex and Oxytocin	Plant (cannabis cigarettes)	Human
Treatment of Cannabinoid Withdrawal in Rhesus Monkeys	Purified (THC) and Endogenous (via AEA via FAAH inhibitors)	Animal
Psychiatric Disorder		
Cannabinoid Regulation of Cognition	Purified (Cannabidiol)	Animal
Cannabidiol Modulation of THC'S Psychotomimetic Effects in Healthy Humans	Purified (Cannabidiol)	Human
Cannabinoid Regulation of Cognition	Purified (Cannabidiol)	Animal
Cannabis, Schizophrenia and Reward: Self-Medication and Agonist Treatment	Synthetic and Plant (Dronabinol & cannabis cigarettes)	Human

Autoimmune disease		
Endocannabinoids, Cannabis, and Neurocognitive Deficits in HIV	Plant (cannabis cigarettes)	Human
Transdermal Delivery of 2-Arachidonoyl Glycerol (2-AG) For the Treatment of Arthr	Endogenous (2-AG)	Animal
Inflammation		
Cannabinoid Epigenomic and Mirna Mechanisms Impact HIV/SIV Disease Progression	Purified (THC)	Animal
Cannabinoid Modulation of Microglial Response to the HIV Protein TAT	Purified and Synthetic (THC and CP55940)	Cell culture and animal models
Pain		
A Randomized, Cross-Over Controlled Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain	Synthetic (Drobinol), Plant (cannabis, vaporized	Human
Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients	Plant (cannabis cigarettes)	Human
Cannabinoid Modulation of Hyperalgesia	Endogenous (AE and 2-AG via URB597 FAAH inhibitor and JZL184 MAGL inhibitor)	Animal
Cannabinoid Receptor Agonists for Treatment of Chronic Pain	Synthetic (CB2 agonist, proprietary)	Animal
Neurogensis and Chronic Cannabinoid Exposure	CB1 Antagonist	Animal
Optimizing Analgesia by Exploiting CB2 Agonist Functional Selectivity	Synthetic (CB2 agonists, proprietary)	Animal
Peripheral FAAH as a Target for Novel Analgesics	Endogenous (AE via FAAH inhibitor (URB937))	Animal
The Effect of Vaporized Cannabis on Neuropathic Pain in Spinal Cord Injury	Plant (cannabis, vaporized)	Human

Note: The analysis was conducted using the internal NIH database (QVR) and was searched using the following: TEXT word string “cannabinoid OR cannabis OR marijuana”; active grants. Grants were manually screened to identify studies in which at least one specific aim included a therapeutic focus.

Appendix D: FDA Approval Process



Appendix E: Recommended Resources and Online Information

For more information regarding CMCR completed studies, visit:
http://www.cmcr.ucsd.edu/index.php?option=com_content&view=category&id=41&Itemid=135

For more information regarding Colorado approved grants, visit:
https://www.colorado.gov/pacific/cdphe/approved-medical-marijuana-research-grants

For more information about NIDA approved studies, visit:
http://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-therapeutic-benefits-cannabis-cannabinoids

For more information regarding NIH sponsored studies, visit:
https://era.nih.gov/nih_and_grantor_agencies/other/query_view_and_report.cfm

For more information regarding the National Center for Natural Research, visit:
http://pharmacy.olemiss.edu/ncnpr/research-programs/cannabis-research/

For more information about the FDA drug approval process generally, visit:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm

For more information about the process of getting FDA approval for cannabis research, visit:
http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm

For more information on the FDA botanical drug approval guidance, visit:
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CenterforDrugEvaluationandResearch/ucm106136.pdf

For more information about NIDA's position and available cannabis supplies, visit:
http://www.drugabuse.gov/drugs-abuse/marijuana/marijuana-research-nida
http://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program

For more information about the DEA's position, visit:
http://www.dea.gov/docs/marijuana_position_2011.pdf

For more information about federal government policies that limit medical cannabis research, visit:
http://www.brookings.edu/~/media/research/files/papers/2015/10/20-war-on-marijuana-research-hudak-wallack/ending-the-us-governments-war-on-medical-marijuana-research.pdf

For more information about institutional review board regulations,
visit:http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html#

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