ASSESSMENT OF THE ENFORCEMENT AND REGULATORY IMPACT ON CANNABINOIDS WITH THE RECENT FOOD AND DRUG ADMINISTRATION'S (FDA) ORDINANCE OVER CANNABIDIOL (CBD) AND THE NEW DRUG ENFORCEMENT ADMINISTRATION (DEA) CONTROLLED SUBSTANCE ACT (CSA) SCHEDULING.

By

FABIAN GILBERTO TEJEDOR ROJAS

(Under the Direction of Randall L. Tackett)

ABSTRACT

Cannabidiol (CBD) has been widely recognized for the beneficial results achieved in multiple pre-clinical and clinical trials. However, the use of marijuana-derived products is still very controversial. This thesis evaluates the impact of the Epidolex® (Cannabidiol) approval by FDA and DEA CSA scheduling with respect to regulatory, enforcement, economic and marketing areas. Similarly, it contrasts the FDA and DEA thinking. The document also summarizes the FDA regulatory requirements for Epidiolex ® (Cannabidiol). The assessment revealed the new status of imports and exports for those products containing CBD (21 CFR 1308 and 21 CFR 1312). Analysis of clinical trials revealed that eight new medical indications using CBD are being studied. Lastly, the study demonstrated that using CBD as a therapy is significantly more expensive than a conventional treatment using Stiripentol and Clobazam for Dravet syndrome.

INDEX WORDS: Cannabidiol, Tetrahydrocannabinol, Cannabinoids, Medical Marijuana, Controlled Substances Act, Enforcement, Regulatory, Clinical Trials, FDA, DEA.

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December 2018

DEDICATION

In memory of my beloved grandmother Matilde, who passed away shortly after I started my program, a very brave woman whom I remember and miss every day.

To God for giving me the strength to successfully complete this program

I would like to dedicate this research paper first and foremost to my parents Olga Lucia and Gilberto from whom I have always received love and support. They who instilled in me the virtues of perseverance and commitment and relentlessly encouraged me to strive for excellence.

To my brother Oscar, sister-in-law Erika and dear nephew Santiago for their joyfulness and enthusiasm.

To my family and friends whom from Colombia often shared encouraging words with me.

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CHAPTER I

Introduction

The therapeutic properties of *Cannabis sativa* have been evaluated since the early 19th century. The first studies of the therapeutic properties were investigated by the physician, Sir William B. O'Shaughnessy. These initial studies assessed the therapeutic effects of *Cannabis sativa* in a variety of conditions and disorders that included cholera, rheumatic diseases, delirium tremens and convulsions. [1, 2] The major advances in the history of Cannabis research are represented by the following timeline [1]:

Table 1: Major discoveries in Cannabis research

In 1899, Wood et al. isolated cannabinol from cannabis resin.
In 1932, Cahn elucidated part of the structure of cannabinol.
In 1940, Todd and Adams et al. fully elucidated and synthetized cannabinol in the United States. This was one of the steps that marked the era of cannabis research.
In 1964 the structure of THC was elucidated by Gaoni and Mechoulam.
In 1988 Howlett's group identified the THC binding sites in the brain.
In 1990 Matsuda et al. cloned for the first time the Cannabinoid 1 receptor (CB1R).
In 1992 Mechoula's group in collaboration with Petwee's group identified the first endocannabinoid known as anandamide.
In 1993, the second receptor of Cannabinoids was cloned by Munro et al.

In 1994, Rinaldi-Carmona et al. at Sanofi developed the first Cannabinoid 1 receptor (CB1R) antagonist called Rimonabant.
In 1995, Mechoulam's group and Waku's group identify the second endocannabinoid known as 2-arachidonylglycerol (2-AG).
In 1996, Cravatt et al. cloned the first endocannabinoid enzyme, fatty-acid amide hydrolase (FAAH).
In 1998, Di Marzo et al. proposed the theory of interactions between endocannabinoids and vanilloid receptors (TRPV).
Between 1999 and 2000, the activation of the anandamide's vanilloid receptors was proposed by Zygmunt and Smart et al.
In 2003 Bisogno et al. cloned the first endocannabinoid-biosynthesizing enzymes.
In 2005, the Aberdeen group discovers an allosteric site on CB1 receptors, the same year, Sativex ® was approved for sale in Canada and regulatory approval was filled in order to obtain marketing approval for Rimonabant in the USA.

Cannabis sativa, Cannabis indica and *Cannabis ruderalis* are three subspecies of *Cannabis. Cannabis ruderalis* is normally not evaluated because of the morphology and low-content of therapeutic components. It would be laborious to extract the active ingredients, and growers opt not to cultivate it because of the small size and short stature of the plant. However, the other two species have been highly evaluated. *Cannabis sativa* is preferred by cultivators because the plants tend to be taller and skinnier, contain longer and thinner leaves and the active ingredients are found in higher proportions. [2, 3, 4] In manufacturing and production, hemp is a term widely used to describe the *Cannabis sativa* used for industrial purposes: textiles, paper, oil,

biomass, edible seeds, cosmetics etc. It is grown in such a way that the plant contains no more than 0.3 percent tetrahydrocannabinol (THC). [4, 5, 6]

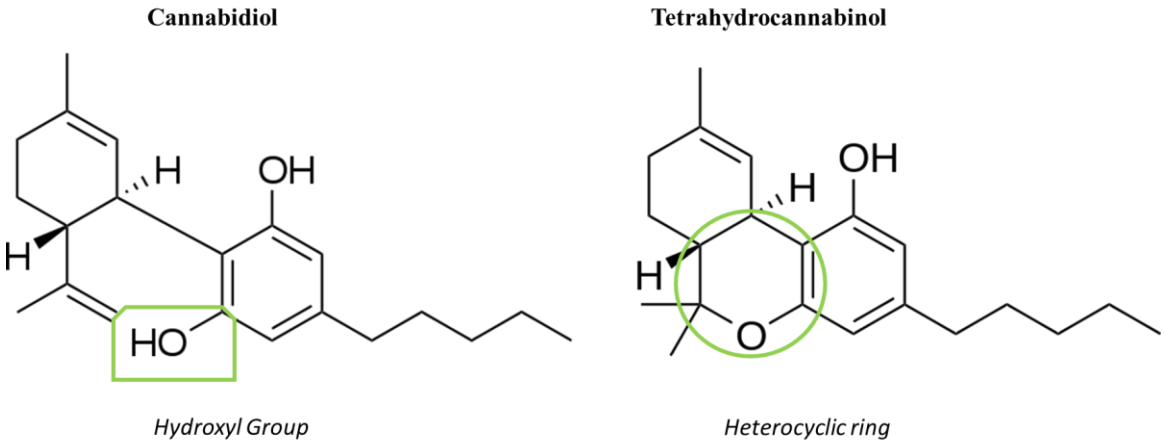

Figure 1: Cannabinoids structural comparison

Two cannabinoids are documented to be the major components of *Cannabis sativa* and attributed to most of the effects of the plant: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Chemically, they are considered isomers. Both have a molecular mass of 314 g/mol. Structurally, they differ in that cannabidiol contains a hydroxyl group and tetrahydrocannabinol contains a heterocyclic ring as shown in Figure 1. The changes in the molecular structures confer the compounds different affinities for protein G coupled- cannabinoid receptors. [3,7,8]

Cannabinoids (THC and CBD) pharmacology

Cannabinoid 1 receptors (CB1R) and Cannabinoid 2 receptors (CB2R) are expressed in humans and are known to mediate the responses caused by the interaction with CBD or THC. CB1Rs are primarily localized in the brain, while CB2Rs are mostly localized in immune cells,

spleen and the gastrointestinal system. [3,9] These cannabinoid receptors are normally mediated by the endogenous neurotransmitters – also known as endocannabinoids: Anandamide (AEA) and 2-arachidonylglycerol (2-AG). These molecules maintain homeostasis and avoid an excess of neuronal activity by acting as retrograde synaptic messengers. As shown in Figure 2, an increase in intracellular calcium promotes the release of the two endocannabinoids into the synaptic space. Subsequently, cannabinoid transporters facilitate the diffusion of endocannabinoids for their degradation. Once in the intracellular space, fatty-acid amide hydrolase (FAAH) performs the enzymatic degradation. The effect of CB1R in the brain is inhibitory; it affects the release of the neurotransmitters dopamine, gamma-aminobutyric acid (GABA), glutamate, serotonin, noradrenalin and acetylcholine. These neurotransmitters mediate the cognitive functions as well as the pain and motor responses. Moreover, the effect of CB2R on the immune cells modulates cytokine release. [3, 9, 10]

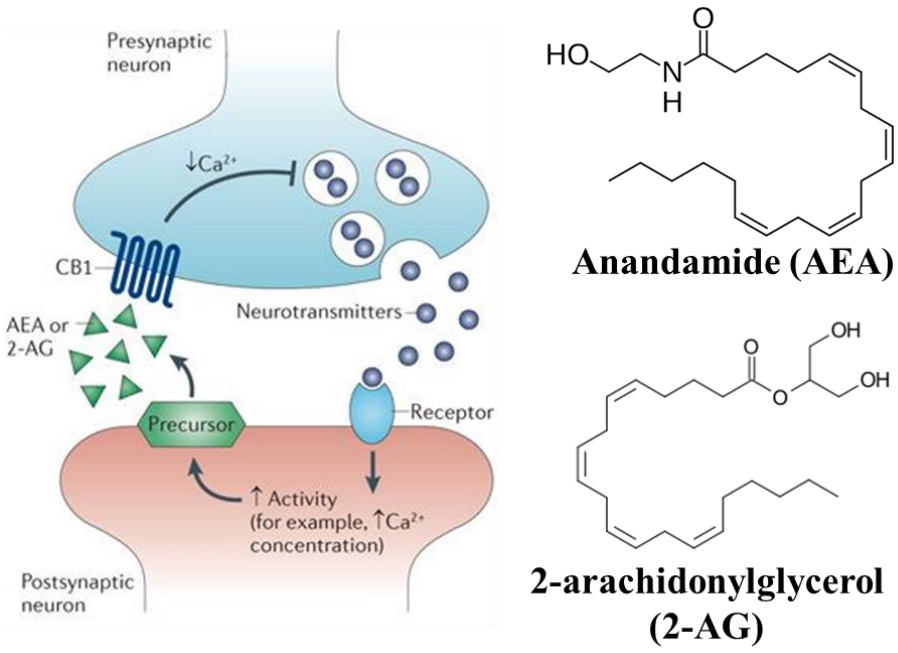

Figure 2: Anandamide (AEA) and 2-arachidonylglycerol (2-AG) modulation

THC is known to be the main psychotropic, analgesic and sedative constituent of *Cannabis sativa*. The molecule acts as a potent partial agonist that binds to the CB1R. The psychoactive response is then an alteration of the release of neurotransmitters within the brain. Homeostasis becomes unstable and glutamate, dopamine and acetylcholine are increased in the synaptic cleft. The mechanism of action is believed to be due to a reduction of GABA. Thus, those neurons that release glutamate, dopamine and acetylcholine are not regulated.[3, 8, 10]

In 1970, Raphael Mechoulam discovered that CBD and other cannabinoids do not possess psychoactive properties. After a series of studies, CBD was attributed to be responsible for most of the beneficial therapeutic effects. CBD has a low affinity for cannabinoid receptors. However, CBD acts as a negative allosteric modulator of CB1R. Because of its interaction with the CB1R, CBD is able to regulate the psychotropic effects of THC. When the shape of CB1R is altered by the allosteric effect of CBD, THC is unable to bind to the site, and therefore the psychoactive effect is somehow counterbalanced. Without the activation of THC, the signal of CB1R is not able to inhibit adenylyl cyclase activity, close voltage mediated calcium channels or open potassium channels.

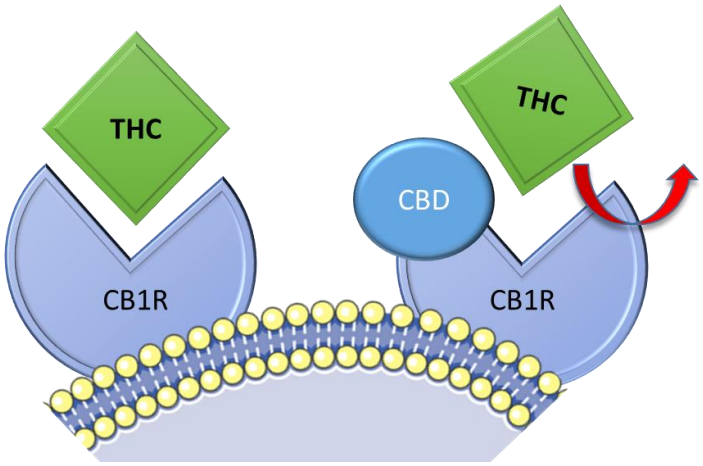

Figure 3: CBD allosteric modulation in CB1R

CBD shows low affinity for CB2R but it regulates the FAAH enzymatic degradation of anandamide by targeting the uptake. CBD has agonistic properties in the 5-hydroxytryptamine receptor (5-HT1A), which are located in areas of the brain that are implicated in the control of mood, cognition and memory. The response obtained by the interaction of CBD and 5-HT1A is the induction of anxiolytic-like effects and mediation of the adaptation to stress. [1, 13, 14, 15] CBD is an agonist of the transient receptor potential vanilloid type 1 (TRPV1) receptors – also known as the capsaicin receptors. These nonselective cation channel receptors are responsible for vasodilation and inflammation when stimulated. The result of the interaction of CBD and TRPV1 receptors is an antihyperalgesic effect. [1, 16] The mechanism of action is attributed to a reduction of the neuronal hyperexcitability and inflammation through regulation of the intracellular calcium via G protein-coupled receptor 55 (GPR55) and TRPV1 channels and modulation of adenosine-mediated signaling. [17] The exact mechanism on how CBD exerts the anticonvulsant therapies in patients with Dravet syndrome and Lennox-Gastaut syndrome is unknown. The anticonvulsant

effects are not attributed to an interaction with cannabinoid receptors since CBD has such low affinity for those receptors.

GW Pharmaceuticals: Epidiolex (Cannabidiol)

GW Pharmaceuticals is the proprietary firm of the oral formulation Epidiolex (Cannabidiol). GW Pharmaceuticals is a biopharmaceutical company focused on discovering, developing and commercializing novel therapeutics based on cannabinoids. The headquarters are located in London, United Kingdom, but they have a U.S. subsidiary, Greenwich Biosciences, located in Carlsbad, California. [18, 19] The characteristics of Epidiolex (Cannabidiol) are described in the labeling as follows: the formulation is a clear, colorless to yellow liquid solution that contains Cannabidiol at a concentration of 100 mg/mL. Epidiolex's pharmaceutical presentation is a 100 mL amber vial (with 2 reusable 5 mL syringes). The formulation contains dehydrated alcohol, sesame seed oil, strawberry flavor and sucralose as the inactive ingredients. [20]

According to the labeling, the recommended starting dosage of Epidiolex (Cannabidiol) is 2.5 mg/kg taken twice daily (total of 5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (total 10 mg/kg/day). However, based on individual clinical response and tolerability, the dosage can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (total 20 mg/kg/day). [20] The product comes with a medication guide and instructions directed to the user for better understanding. In addition, Epidiolex (Cannabidiol) labeling information portrays the most common adverse reactions at a concentration of 10% or more. These adverse reactions were reported to be: somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, rash, insomnia, sleep disorder and poor-quality sleep and infections when compared to placebo. [20]

Epidiolex (Cannabidiol) was granted a fast track designation for Dravet syndrome since the drug is the first FDA treatment available and approved for patients with Dravet syndrome. In addition, Epidiolex (Cannabidiol) received orphan drug designation for both the Dravet syndrome and Lennox-Gastaut syndrome.

The controversy pertaining to the use of CBD in the United States is based on the fact that Cannabidiol is categorized as a Schedule I controlled substance within the Controlled Substance Act (CSA). Adding to this controversy, there is a stigmatization of Cannabidiol because of the recreational consumption of marijuana. There is also a lack of controlled studies demonstrating the safety and efficacy of Cannabidiol as an alternative to current therapies. Adding to this controversy, the enforcement and regulatory oversight involves multiple federal agencies (FDA and DEA). As such, the process is burdensome and lengthy.

The current thesis is intended to assess the impact of FDA Epidolex® (Cannabidiol) approval and the Drug Enforcement Administration (DEA) Controlled Substances Act (CSA) scheduling over the regulatory, enforcement, economic and marketing areas.

CHAPTER II

Role of the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA)

The FDA plays a critical role in the regulation and enforcement of cannabinoids. The mission of the Agency states that "The FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation". [20] They ensure that the products released to the market purport a positively balanced benefit-risk assessment. The Agency has different centers with jurisdiction over certain specialties. In the case of Epidiolex, the Center for Drug Evaluation and Research (CDER) oversees the regulatory and enforcement actions related to Cannabidiol. Since 1938, CDER oversees that every new drug has an approved New Drug Application (NDA) before being commercialized within the United States.[21]

The Drug Enforcement Administration (DEA) has an important role in the regulation of cannabinoids. Their mission reflects that the DEA is responsible for "enforcing the controlled substances laws and regulations of the United States and bring to the criminal and civil justice system of the United States, or any other competent jurisdiction, those organizations and principal members of organizations, involved in the growing, manufacture, or distribution of controlled substances appearing in or destined for illicit traffic in the United States; and to recommend and support non-enforcement programs aimed at reducing the availability of illicit controlled

substances on the domestic and international markets."[22] Consequently, the focus of the DEA is primarily punitive.

In the efforts to prevent drug abuse and drug dependence, the United States Congress enacted the Comprehensive Drug Abuse Prevention and Control Act of 1970. Tile II of the Act includes a statute that regulates the manufacture, importation, possession, use, and distribution of certain substances. This statute is designated the Controlled Substances Act (CSA). The 1970 act was part of an amendment to the Public Health Service Act (PHSA). It created five schedules that comprise the regulated substances into Schedules I-V; the last one (Schedule V) being the most lenient and flexible. [23, 24]

DEA Drug Scheduling and FDA contribution

The classification is based upon three aspects that impact human health as depicted in Figure 4: (1) Accepted medical applications in the U.S, (2) Safety and potential for addiction and (3) Abuse potential.[25]

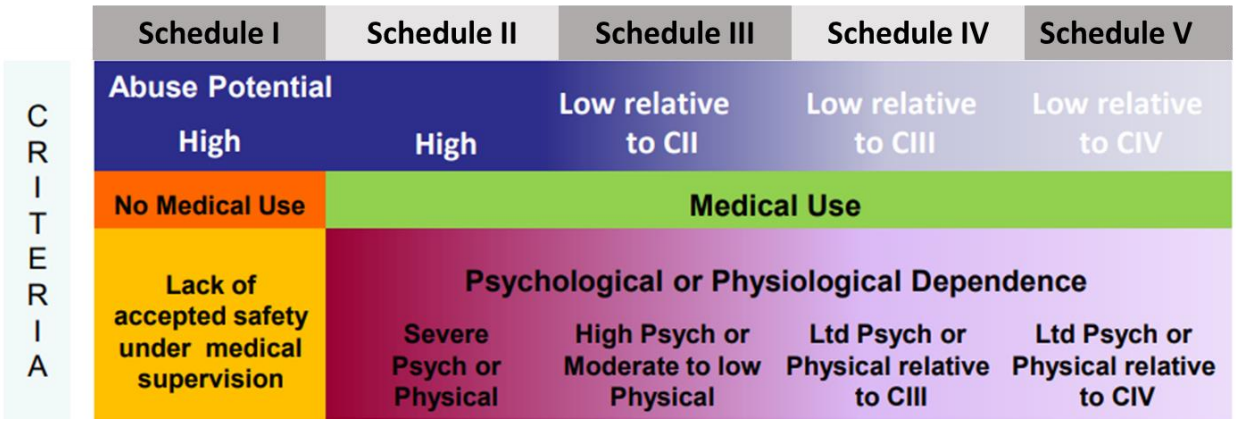

Figure 4: Criteria for scheduling a substance within the Controlled Substance Act

Schedule I Controlled Substances are characterized as not having any accepted medical use in the United States. Schedule I substances are unsafe for use under medical supervision and have a high potential for abuse. Some of the substances listed within the Schedule I category are heroin, LSD, marijuana, peyote, and 3,4-methylenedioxymethamphetamine (MDMA or ecstasy).[26]

Schedule II Controlled Substances possess a high potential for abuse which may lead to severe psychological or physical dependence. The substances in this category may have a currently accepted medical use in the United States or a currently accepted medical use with severe restrictions. Some of the substances listed within Schedule II narcotics include (but are not limited to): hydromorphone, methadone, meperidine, oxycodone and fentanyl and narcotics such as: morphine, opium, codeine, and hydrocodone. [26]

Schedule III Controlled Substances have a moderate potential for abuse (less than the substances in Schedules I or II). Substances within this category can develop moderate to low physical dependence or high psychological dependence. The substances in this category have a currently accepted medical use in the United States. Narcotics of the Schedule III contain no more than 90 milligrams of codeine per dosage unit (i.e Tylenol –Codeine). Some of the Schedule III non-narcotics are: ketamine and anabolic steroids. [26]

Schedule IV Controlled Substances possess a low potential for abuse relative to substances in Schedule III. The drugs have a currently accepted medical use in the United States. Some of the Schedule IV substances are: alprazolam, clonazepam, diazepam and lorazepam [26]

Schedule V Controlled Substances have a low potential for abuse relative to substances listed in Schedule IV. Those substances are, in most cases, preparations that contain limited amounts of certain narcotics. Some of the Schedule V examples are: cough preparations like

Robitussin, Phenergan with Codeine and Retigabine. Within this category is the newly scheduled Epidiolex (Cannabidiol). [26]

In order to categorize the substance, there is an eight factor analysis that allows the agencies to determine the best scheduling. Section 201(c) of the Comprehensive Drug Abuse Prevention and Control Act requires the Department of Health and Human Services (HHS) establishes the criteria for classification of substances. The eight-factor analysis contains the following requirements [25, 27]:

1. Actual or relative potential for abuse

2. Scientific evidence of pharmacological effect

3. State of current scientific knowledge regarding the substance

4. History and current pattern of abuse

5. Scope, duration, and significance of abuse

6. Risk to the public health

7. Psychic or physiological dependence liability

8. Immediate precursor of a substance already controlled

The CSA was created to align the United States practices with the international requirements of the Single Convention on Narcotic drugs of 1961. The convention was created to fight drug abuse with international cooperation. In this convention, two roles were established for international action. One, the convention is intended to limit the possession, use, trade in, distribution, import, export, manufacture and production of drugs exclusively for medical and

scientific purposes. Secondly, the convention has the task of fighting drug trafficking by aiming and weakening drug traffickers. [28]

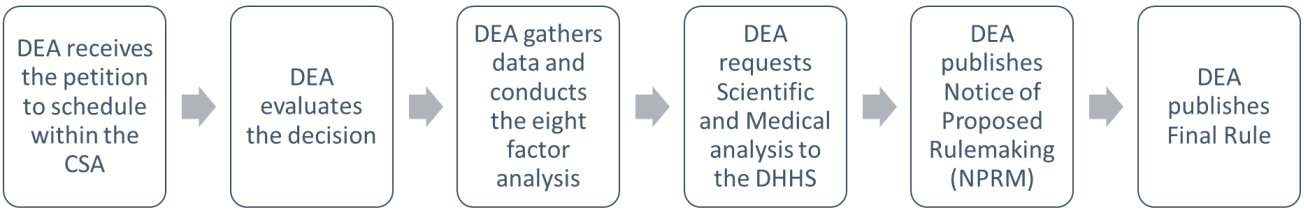

Figure 5: Role of the DEA in CSA scheduling process

The DEA has primary responsibility when scheduling a substance. Figure 5 depicts the process that a substance goes through when receiving a scheduling. The DEA decides whether to accept or decline the petition from the FDA. Officials from the DEA conduct an eight factor evaluation and compare it with the concept given by the Department of Health and Human Services (HHS). The DEA then publishes the notice of proposed rulemaking, and, after all the administrative process, the final rule is published in the federal register. [25]

The FDA also participates in the scheduling process by providing an eight-factor analysis and rationale for the scheduling in a scientific and medical summary. Initially, the request is directed to the Department of Human Health services through the Assistant Secretary of Health. The FDA then goes through the center that holds jurisdiction over the drug. In the case of Epidiolex (Cannabidiol), it is the Center for Drug Evaluation and Research (CDER). Offices within the CDER – the Office of New Drugs (OND), Office of Surveillance and Epidemiology (OSE) and Office of the Chief Counsel (OCC) – aid with the medical and scientific evaluation. The National

Institutes of Health (NIH) also provides important insight in the final concept of the Epidiolex evaluation request through the National Institute on Drug Abuse (NIDA) assessment.[25] The NIDA participates in additional stages of the research. They are the source that provides research grade marijuana from a grow research secure facility (Located in the University of Mississippi) for scientific studies.[29] Some of the regulatory provisions required by each schedule are summarized in Figure 6. These requirements are followed and overseen by both agencies.[25]

	Schedule I	Schedule II	Schedule III	Schedule IV	Schedule V
Registration	Required	Required	Required	Required	Required
Recordkeeping	Separate	Separate	Readily Retrievable	Readily Retrievable	Readily Retrievable
Distribution Restrictions	Order Forms	Order Forms	Records Required	Records Required	Records Required
Dispensing Limits	Research use only	Rx: written No Refills	Rx: written or oral Refills with MD's authorization	Rx: written or oral Refills with MD's authorization	OTC (Rx drugs limited to MD's order
Manufacturing Security	Vault/Safe	Vault/Safe	Secure Storage	Secure Storage	Secure Storage
Manufacturing Quotas	Yes	Yes	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)

Figure 6: Regulatory requirements for each schedule

Epidiolex (Cannabidiol) and the role of both agencies

GW Pharmaceuticals submitted a New Drug Associated (NDA) to the FDA in order to market the drug within the United States. On June 25, 2018, Epidiolex was approved by the FDA for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.[25] The drug was evaluated by the Peripheral and Central Nervous System Drugs Advisory Committee and FDA reviewers. [19]

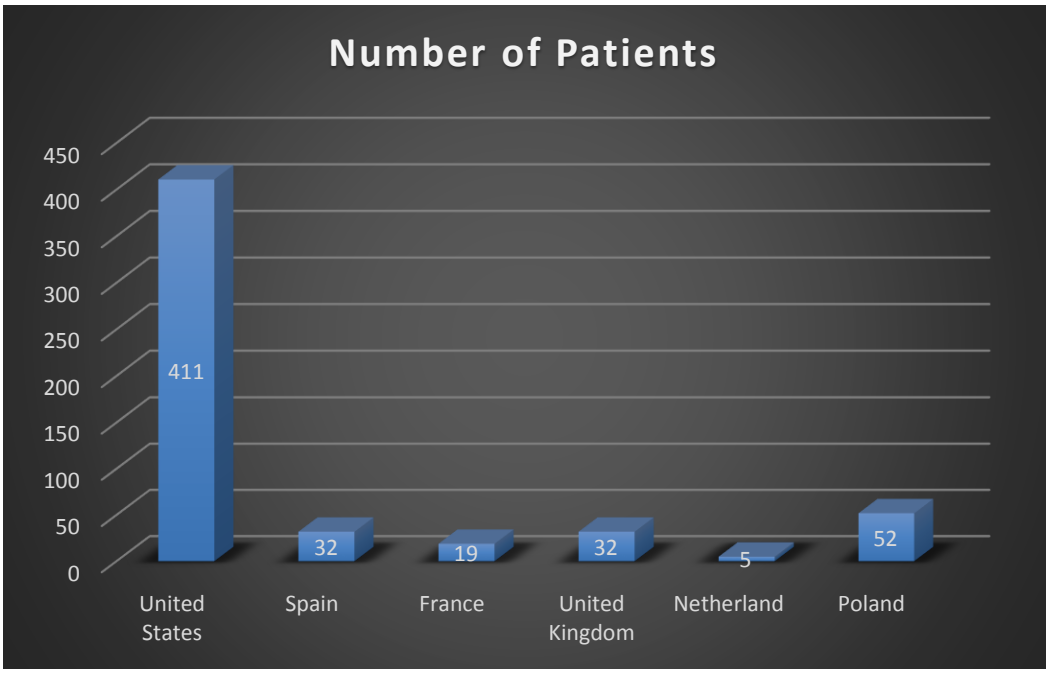

Figure 7: Total number of Epidiolex clinical trial patients divided by region

The approval was granted due to the demonstration of safety and efficacy in four clinical trials: clinical trial 1/NCT02224560, clinical trial 2/NCT02224690, clinical trial 3/NCT02091375, clinical trial 4/NCT02091375. The trials resulted in an evaluation of 550 patients with Lennox-Gastaut or Dravet syndromes and were conducted at 58 sites in Europe and the United States. [19, 30] Figure 7 represents the total number of participants in the clinical trials used to support the NDA. Of those 550 individuals evaluated, 411 patients were treated within the United States territory. It is significant to note that 25% of the patients were from five European countries. Most of the patients were from the U.S and represented the 75%.[30] Even though conducting a clinical trial in the United States is a very rigorous process, the numbers reflect the desire of the firm to obtain quality information and provide adequate, substantial evidence to the FDA.

In summary, the FDA is charged with regulating clinical trials and the introduction of new drugs into the market. The DEA establishes the schedule of the controlled substance. In addition, the DEA is responsible for establishing production quotas for drugs with potential for abuse (drugs specified within the CSA) to prevent their diversion to illicit channels.[31] The DEA also oversees the security and restriction regulatory requirements. In brief, this is how both agencies work in partnership to protect and promote the public health and enforce the controlled substances laws and regulations of the United States.

CHAPTER III

Enforcement Impact

Research Questions

Are the enforcement activities negatively/positively impacted by the new FDA approval of Epidiolex (Cannabidiol)?

Subsidiary questions

What amendments have been made in the Code of Federal Regulations changing the scope of the DEA activities?

Are there any criminal-cases where the consumption of controlled substances has interfered with the prosecution of the criminal offenses?

Federal Register Final rule and changes in the Code of Federal Regulations

In order to determine the changes in the DEA and FDA enforcement scope, the Official Journal of the Federal Government of the United States (Federal Register) was examined. The Federal Register contains information regarding DEA and FDA rules, proposed rules and public notices.

A rule is expected to be proposed in order to encompass and update the changes suggested and accomplished by FDA or DEA authorities (Figure 8). Initially, the DEA was given a 90 day-window to establish a decision regarding the classification of Epidiolex (Cannabidiol) within the

CSA act. On September 28, 2018, the DEA expressed the final rule order – Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol; Corresponding Change to Permit Requirements. [32] With the approval of this rule, the Code of Federal Regulations (CFR) is required to be amended in order to adopt the new dispositions derived from the approval of Epidiolex.

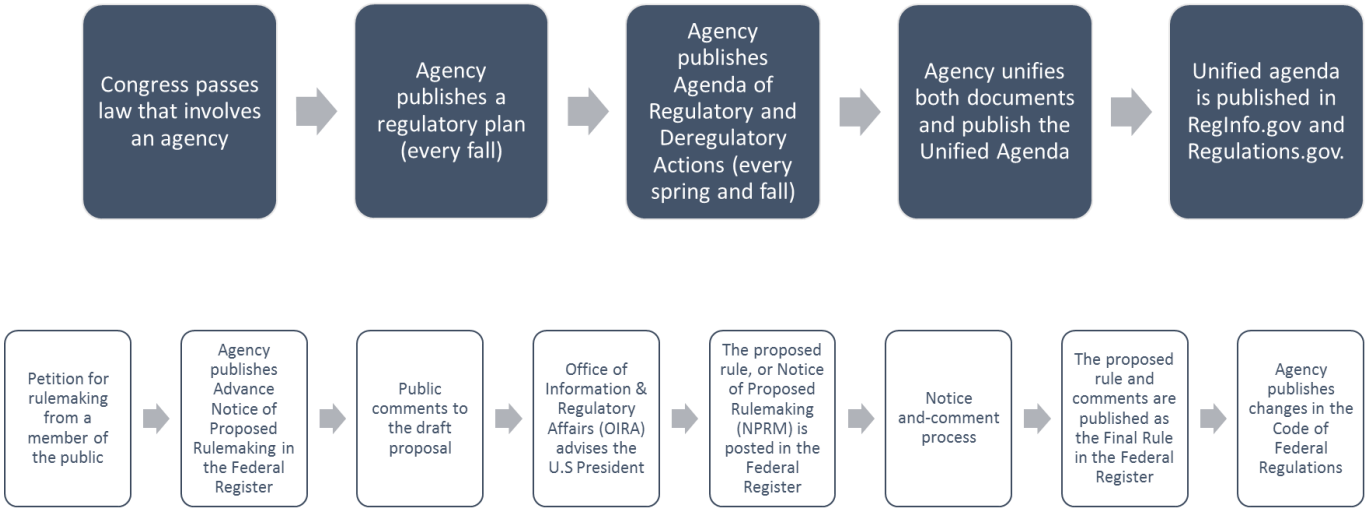

Figure 8: Summary of the Rulemaking process

The modifications in title 21 of the Code of Federal Regulations are intended to include the following two main provisions in parts 1308 and 1312 [32]:

1. Within the title 21 CFR Part 1308, the inclusion of paragraph in 21 CFR 1308.15 Schedule V to state "(f) Approved Cannabidiol drugs. (1) A drug product in finished dosage formulation that has been approved by the U.S. Food and Drug Administration that contains Cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-

pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols"

The amendments also direct changes to the provisions of the administrative practice and procedure, drug traffic control and reporting and recordkeeping requirements.

2. Within title 21 CFR Part 1312, the inclusion of paragraph (b) in 21CFR 1312.20 Schedule III, IV, and V non-narcotic controlled substances requiring an import and export permit to read as following: "The following Schedule III, IV, and V non-narcotic controlled substances have been specifically designated by the Administrator of the Drug Enforcement Administration as requiring import and export permits pursuant to sections 201(d)(1), 1002(b)(2), and 1003(e)(3) of the Act (21 U.S.C. 811(d)(1), 952(b)(2), and 953(e)(3)). (b) A drug product in finished dosage formulation that has been approved by the U.S. Food and Drug Administration that contains Cannabidiol (2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol) derived from cannabis and no more than 0.1 percent (w/w) residual tetrahydrocannabinols."

The amendments are intended to change the provision of the administrative practice and procedures, drug traffic control, exports, imports and reporting requirements. With these changes in the stipulations of both 1308 and 1312 of the title 21 of the Code of Federal Regulations, the DEA enforcement activities are reshaped, the schedule of Epidiolex (Cannabidiol) is now categorized within Schedule V, and it lessens the burden of surveillance and examination required for those products within Schedule I. It also creates new requirements for permits to export and import. It is imperative to note that the change in the schedules include only the specific formulation of Epidiolex. CBD remains within the CSA Schedule I. In the DEA Federal Register,

the Agency specifies that materials that contain THC and CBD extracted from the cannabis plant are within the listings of extracts and tinctures of cannabis for purposes of the Single Convention. As a consequence of that implication, those bulk materials that are used by the manufacturing of the Epidiolex formulation are still within the Schedule I of the CSA, and thus will be subject to the enforcement actions from the DEA. The prosecution of activities is now more complex than ever because of the difficulty of ensuring compliance with the single convention.

DUI-Enforcement: A case-study for the State of Georgia

More enforcement areas are impacted by adjustments to the law. In order to evaluate obstacles that arise when prosecuting criminal cases, a web search of DUI public records dockets and cases within the State of Georgia was completed. For the purposes of this research, the examination was limited to the State of Georgia by analyzing the Court of Appeals of Georgia and the Supreme Court of Georgia public records and was performed through a retrospective analysis. [33]

In the United States, the term Driving Under the Influence refers to driving under the influence of alcohol, drugs, or a combination of alcohol and drugs.[34] Some states have a zero-tolerance (or per se) policy when referring to that criminal charge; including when it is related to prescription medications. [35] Table 2 depicts the status of the use of cannabis by state [36] and also relates the panorama of the zero-tolerance standing. It is key to understand in the following analysis that the zero-tolerance policy makes it illegal to operate a motor vehicle with any measurable amount of specified drugs in the body.

As of January 2018, a total of twelve states have a zero-tolerance law. Nine states (AZ, D.C., GA, IL, IN, OK, RI, SD and UT) have a zero-tolerance (per se) policy for THC, meaning

that it is illegal to have any amount of the drug and/or its metabolites when operating a motor vehicle. Three states (IA, MI and WI) have a zero-tolerance policy specific for THC (does not include the metabolites), meaning that it is illegal to have any amount of THC when operating a motor vehicle. [34, 35, 36]

Table 2: Legal status of Cannabis in the United States

State	St.	Legal Medical Use?	Legal Recreational Use?	Zero tolerance law
Alabama	AL	no	no	no
Alaska	AK	yes	yes	no
Arizona	AZ	yes	no	THC and metabolites
Arkansas	AR	yes	no	no
California	CA	yes	yes	no
Colorado	CO	yes	yes	yes
Connecticut	CT	yes	no	no
District of Columbia	D.C	yes	no	THC and metabolites
Delaware	DE	yes	yes	no
Florida	FL	yes	no	no
Georgia	GA	no	no	THC and metabolites
Hawaii	HI	yes	no	no
Idaho	ID	no	no	no
Illinois	IL	yes	no	THC and metabolites
Indiana	IN	no	no	THC and metabolites
Iowa	IA	no	no	THC
Kansas	KS	no	no	no
Kentucky	KY	no	no	no
Louisiana	LA	no	no	no
Maine	ME	yes	yes	no
Maryland	MD	yes	no	no
Massachusetts	MA	yes	yes	no
Michigan	MI	yes	no	THC
Minnesota	MN	yes	no	no
Mississippi	MS	no	no	no

State	St.	Legal Medical Use?	Legal Recreational Use?	Zero tolerance law
Missouri	MO	no	no	no
Montana	MT	yes	no	no
Nebraska	NE	no	no	no
Nevada	NV	yes	yes	no
New Hampshire	NH	yes	no	no
New Jersey	NJ	yes	no	no
New Mexico	NM	yes	no	no
New York	NY	yes	no	no
North Carolina	NC	no	no	no
North Dakota	ND	yes	no	no
Ohio	OH	yes	no	no
Oklahoma	OK	no	no	THC and metabolites
Oregon	OR	yes	yes	no
Pennsylvania	PA	yes	no	no
Rhode Island	RI	yes	no	THC and metabolites
South Carolina	SC	no	no	no
South Dakota	SD	no	no	THC and metabolites
Tennessee	TN	no	no	no
Texas	TX	no	no	no
Utah	UT	no	no	THC and metabolites
Vermont	VT	yes	no	no
Virginia	VA	no	no	no
Washington	WA	yes	yes	no
West Virginia	WV	yes	no	no
Wisconsin	WI	no	no	THC
Wyoming	WY	no	no	no

A few federal laws are ambiguous and improperly designed to be well-suited to all states. That effect leads to misinterpretation or failed enforcement of state laws. The twelve states where the zero-tolerance law includes THC, particularly those nine with the zero-tolerance per se policy, are expected to experience complications when enforcing DUI-drug related offenses. There are

several cases in other states than the State of Georgia that expressly show the problematic effect when seeking the prosecution of a DUI-related crime and the consumption of cannabis. Aligned with the strategy, the search of public records in the state of Georgia yielded a few cases of interest. Nevertheless, two of those cases are recognized as the most polemic and problematic when enforcing DUI laws.

In the criminal case *Love v. State*, 517 S.E.2d 53 (1999). the Georgia Supreme Court held that the zero-tolerance policy (per se) DUI drugs statute's disparate treatment of legal versus illegal marijuana users was unconstitutional. [37] The court drew an arbitrary distinction concerning the rights of legal and illegal users of marijuana finding it unfair and a violation of the equal protection clauses. The equal protection premise states that a governmental entity may not deny an individual the equal protection of the laws. In other words, they must treat an individual in the same way as others in similar conditions and circumstances. [38] In the case *Love v. State*, 517 S.E.2d 53 (1999), they contended that legal users of marijuana could be convicted only if their use rendered them incapable of driving safely. Whereas those who illegally used marijuana faced prosecution for having any amount of marijuana in their system even if they were not found impaired.[35, 36, 37 38]

In a similar case, *Sandlin v. State*, 307 Ga. App. 573 (2011), the Georgia Court of Appeals used the *Love v. State*, 517 S.E.2d 53 (1999) Georgia Supreme Court rationale to hold that the zero- tolerance (per se) DUI-Drugs statute was unconstitutional, by means of representing a violation of the equal protection premises. In this case, the legal users of alprazolam were implicated in the disparate treatment of legal versus illegal users. The court overturned the defendant's conviction because alprazolam is a controlled substance within the Schedule IV that can be legally prescribed. [39, 40]

The State of Georgia is one of those states where the enforcement of DUI's is mandated by the zero tolerance (per se) policy. The Official Code of Georgia Annotated (O.C.G.A.) title 40 chapter 6-391 contains information regarding the DUI alcohol, drugs, or other intoxicating substances penalties and directives. The code states that [41]:

"(a) A person shall not drive or be in actual physical control of any moving vehicle while:

(1) Under the influence of alcohol to the extent that it is less safe for the person to drive;

(2) Under the influence of any drug to the extent that it is less safe for the person to drive;

(3) Under the intentional influence of any glue, aerosol, or other toxic vapor to the extent that it is less safe for the person to drive;

(4) Under the combined influence of any two or more of the substances specified in paragraphs (1) through (3) of this subsection to the extent that it is less safe for the person to drive;

(5) The person's alcohol concentration is 0.08 grams or more at any time within three hours after such driving or being in actual physical control from alcohol consumed before such driving or being in actual physical control ended; or

(6) Subject to the provisions of subsection (b) of this Code section, there is any amount of marijuana or a controlled substance, as defined in Code Section 16-13-21, present in the person's blood or urine, or both, including the metabolites and derivatives of each or both without regard to whether or not any alcohol is present in the person's breath or blood."

State of Georgia-DUI records and Evaluation of the cases

Compiling the 2014-2017 reports from the Georgia Department of Driver Services,[42, 43] the DUI cases related to marijuana as per O.C.G.A. 40-6-391(a)(6) are summarized in Table 3. The chart also depicts the percentage of the cases that increases or decreases with respect of the previous month changes.

Table 3: State of Georgia DUI-Marijuana related O.C.G.A. 40-6-391(a)(6) offenses

Year	DUI Convictions	DUI-Marijuana related*	Percentage of Cases	Percentage of Increase/Decrease (Numbers)
2014	28909	176	0.609	N/A
2015	28035	181	0.646	2.8409
2016	24603	170	0.691	-6.0773
2017	22955	162	0.706	-4.7059
Average	26126	172		
SD	2437.4	7.1		

On average, in the State of Georgia, 172 DUI cases end up with prosecution and convictions under the premises of 40-6-391(a)(6) DUI-marijuana related offenses. The number of cases related to marijuana convictions had a low variability in the years studied but a tendency to decrease within the past three years. The percentage of cases reveals the actual panorama of the DUI-marijuana related cases over the years (Figure 9). Although the percentage of cases increases over the years, the numbers are small when compared to the total number of drug convictions.

However, those numbers are still meaningful taking into account that the prosecution struggles every day in trying to successfully pursue charges in relation to 40-6-391(a)(6) DUI-marijuana related offenses. [42, 43]

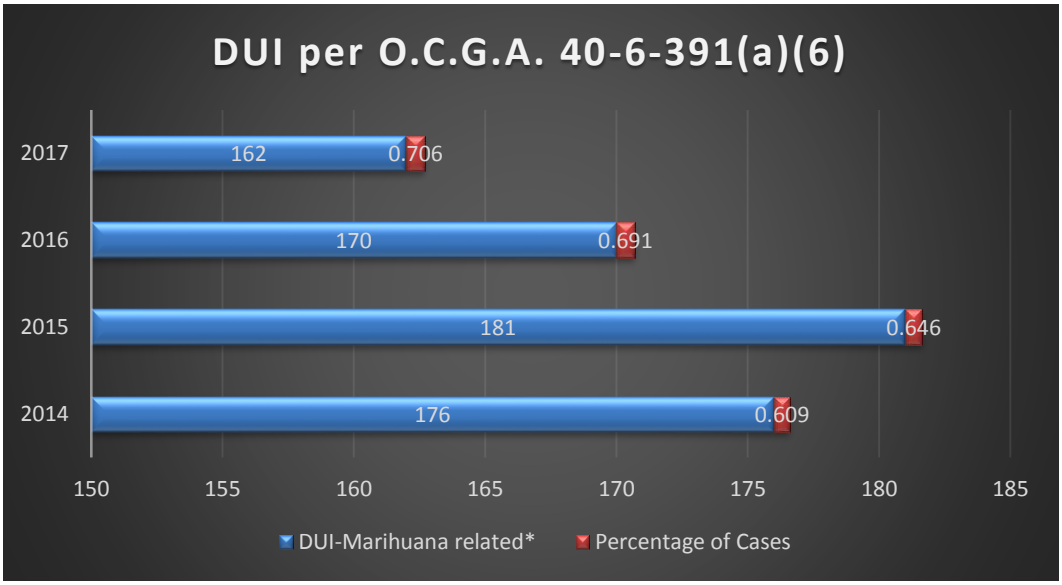

Figure 9: Georgia DUI-Marijuana related O.C.G.A. 40-6-391(a)(6)

In the State of Georgia, prosecutors are legally authorized to use evidence from specimens such as blood, urine and other bodily substances to determine marijuana related convictions. However, in most of the cases, the prosecution uses evidence of impairment (1) if the person admits the use of a drug; (2) if the personal appearance indicates drug use; (3) if the person presents redness dilated or constricted pupils; (4) slurred speech; (5) irregular driving; (6) poor field sobriety test performances and even the presence of drugs in the vehicle are reasons that the prosecution justifies impairment.[40] Still, as the numbers expressed, the prosecution outcomes are not significantly successful.

Compiling the 2014-2017 reports from the Georgia Department of Driver Services (DDS)[42, 43,] the DUI cases related to drugs as per section O.C.G.A. 40-6-391(a)(2) are summarized in Table 4. The table also depicts the percentage of the cases that increased or decreased with respect of the previous month changes.

Table 4: State of Georgia DUI-drug related O.C.G.A. 40-6-391(a)(2) offenses

Year	DUI Convictions	DUI-Drug	Percentage of Cases	Percentage of Increase/Decrease (Numbers)
2014	28909	1786	6.178	N/A
2015	28035	1954	6.970	9.4065
2016	24603	1885	7.662	-3.5312
2017	22955	1950	8.495	3.4483
Average	26126	1894		
SD	2437.4	68.0		

On average, 1894 cases of DUI convictions in the State of Georgia were prosecuted as 40-6-391(a)(2) DUI-drug related offenses. The number of cases related to drug convictions show a worrisome panorama. In most recent years, the cases showed a tendency to increase. In the current year 2018, only in 9 months (from January to September) 1436 DUI-drug related cases have taken place.[43] The comparison over the years is depicted in Figure 10. There is a small decrease in 2016 with regards to 2015, but still a significantly high number for the total of cases. Just from 2014 to 2015, the numbers increased from 1786 to 1954. The percentage of the cases portrays the real

increase of cases year by year. Although the DUI-drug related convictions are variable, the number of DUI-convictions tend to decrease.

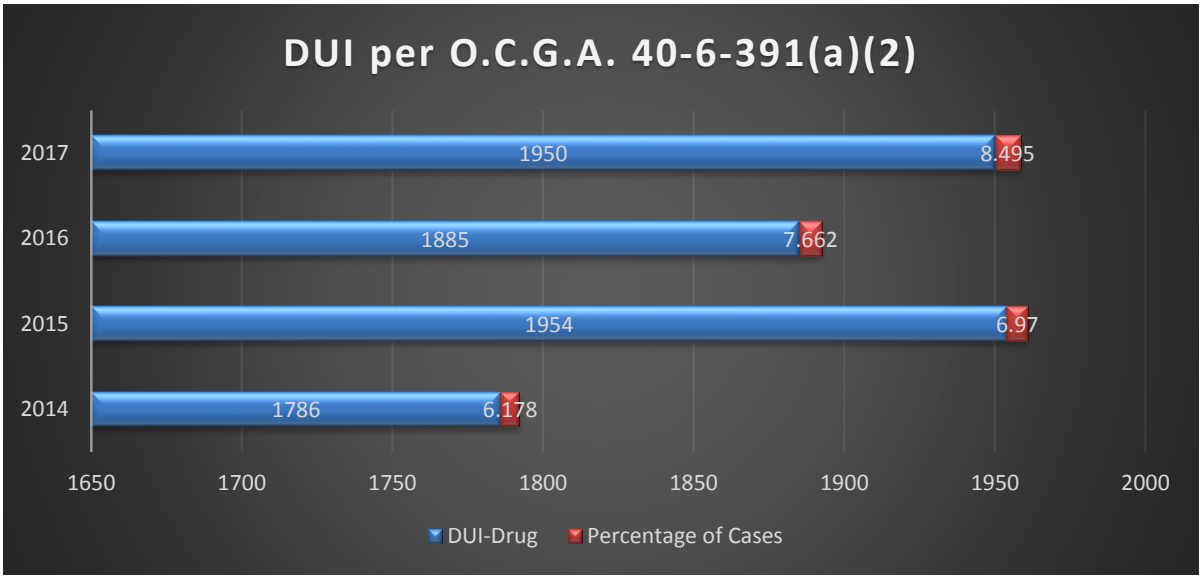

Figure 10: State of Georgia DUI-drug related O.C.G.A. 40-6-391(a)(6) offenses

Both 40-6-391(a)(2) and 40-6-391(a)(6) convictions expose how critical the numbers are. Despite a higher rate than expected, it is thought that most of the cases are dropped or dismissed because of the lack of evidence or because of the legal holding used in court. With the inclusion of Epidiolex (Cannabidiol) in the market, states will need to monitor the scope, application and prosecution of the law. Sooner than expected, the State of Georgia will be compelled to evaluate the discrepancies into the manifests of the DUI-law with respect of the THC content from Epidiolex (Cannabidiol).

It is clear that amendments will be required in the official code (O.C.G.A). Then, the interpretation relies on what changes need to be executed. Perhaps, the State needs to contemplate not just the recent approval of Epidiolex (Cannabidiol) but, rather, a future de-scheduling of

Cannabidiol. The adjustments, for now, need to address the particular content of THC within the formulation of Epidiolex. Both cases *Love v. State*, 517 S.E.2d 53 (1999). and *Sandlin v. State*, 307 Ga. App. 573 (2011) portray disputes in the application of the DUI law. The State of Georgia is advised to adjust the law in order to include Epidiolex (Cannabidiol) as a legal drug. Similarly, states with zero-tolerance per se policies are advised to review their state codes to include Epidiolex (Cannabidiol) as a legal drug. It is imperative to recall when outlining the amendments that the formulation approved by the FDA contains no more than 0.1 percent (w/w) residual tetrahydrocannabinol. Also, it is important to distinguish that because of the lack of affinity for cannabinoid receptors, CBD is a substance that does not possess psychotropic effects, and therefore the driving activities would not be impaired. Lastly, as a reminder to the states, the concentration of THC in the oral formulation of Epidiolex (CBD) can be found within the body of a consumer. Even though, the pharmacokinetics differ from person to person and affect the presence of the drug in the body at different stages, it can still be found by detection methods. For example, if Epidiolex (Cannabidiol) was consumed -at a normal dose, THC could be detected by DUI rapid detection kits, such as oral fluid road test Quantisal Immunoassay LC-MSMS. [44] Even though this positive detection can be a justification of arrest, the case could easily not proceed because of the legal holding arisen in the prosecution of both *Love v. State*, 517 S.E.2d 53 (1999). and *Sandlin v. State*, 307 Ga. App. 573 (2011) cases.

To conclude, the results of both subsidiary questions are inclined to predict unfavorable outcomes. The modifications to the scope of the DEA actions are challenging because of the struggle to ensure the compliance with the international requirements of the single convention on narcotic drugs. Additionally, the prosecution of criminal charges related to drug related DUI-drug offenses could be in jeopardy similarly to the cases reported within the State of Georgia. Thus, as

a consequence of the issues and the two unfavorable determinations, it is appropriate to infer that the enforcement actions will be negatively impacted following the recent approval of Epidiolex (Cannabidiol).

CHAPTER IV

Regulatory Impact

Research Questions

Are the Regulatory activities being negatively/positively impacted by the new FDA ordinance over Cannabidiol (CBD)?

Subsidiary questions

Is there an increase or decrease in clinical trials exploring Cannabidiol?

With the FDA approval of the New Drug Application (NDA), are there new specific regulatory requirements for GW Pharmaceuticals?

Clinical trials evaluation and its regulatory panorama

Clinical Trials.gov is a resource provided by the U.S. National Library of Medicine where new and completed, privately and publicly funded, clinical trials conducted around the world are registered. The variability of clinical trials was assessed using this database in a retrospective analysis. The criteria used to analyze the clinical trials was restricted to a search of studies that contained “Other Terms” Cannabidiol or Epidiolex. Of the 287,766 research studies posted in the entire data base, 167 studies contained the term Cannabidiol. From the 287,766 research studies posted in the entire data base, 17 studies contained the term Epidiolex. Those 17 studies were included within the 167 study sample.

From the 167 studies, a thorough revision and manual inspection was completed. Studies posted in 2018 were designated as potential candidates to be evaluated for the purposes of this study. "First posted" date was the criteria to include or exclude the studies from the sample. After the examination, 26 studies met the criteria required for the evaluation. (Appendix I) [45]

The information was retrieved from the database using October 23, 2018 as an end point. In order to analyze the changes in the number of clinical trials, information from January 2018 to October 2018 was retrieved from the database. Table 5 summarizes the number of new clinical trials categorized by month and a simple descriptive analysis of the percentage increase.

Table 5: Compilation of Cannabidiol Clinical Trials from January – October 2018

Month	Number of new Clinical Trials	Total of Clinical Trials	Percentage Increase (by month)	Cumulative Percentage Increase
January	1	142	0.71	0.71
February	1	143	0.71	1.42
March	4	147	2.84	4.26
April	0	147	0.00	4.26
May	4	151	2.84	7.09
June	3	154	2.13	9.22
July	3	157	2.13	11.35
August	5	162	3.55	14.89
September	3	165	2.13	17.02
October	2	167	1.42	18.44

The number of clinical trials registered in the U.S National Library of Medicine Clinical Trials.gov database have increased drastically in the current year. To date, the clinical trials involving Cannabidiol have increased 18.44%. The database grew from 141 (December 2017) to 167 trials (October 23, 2018) with a significant increase within the last months studied.

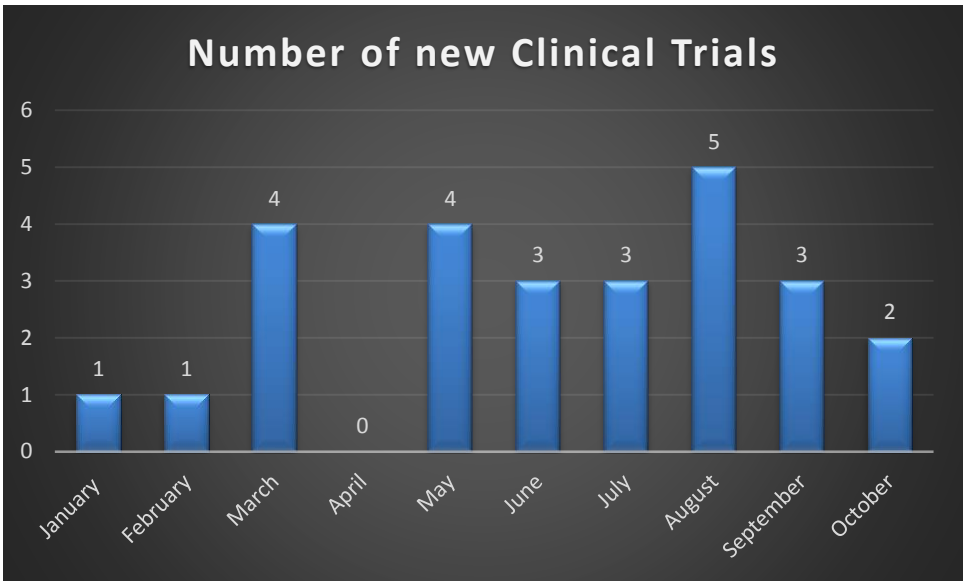

Figure 11: Number of Clinical Trials per month (year 2018)

As observed in Figure 11, August was the month with the highest number of 2018 clinical trials posted (5 new studies, 3.55% increase).:

1. Cannabidiol in Patients with Heart Failure, Failure in AHA/ACC Stages A-C (CAPITAL-AC): This is a Phase I, Single Center, Open-label Study. [46]
2. Cannabis Oil for Chronic Non-Cancer Pain Treatment (CONCEPT): This is a Phase II, Parallel, Multicenter, Randomized controlled trial. [47]
3. Cannabis Oil for Pain in Parkinson's Disease (MDC-CAN-PD): This is a Phase II, Randomized, Open-label, Double-blind, Two-center Study to Evaluate the Tolerability, Safety and Dose-finding of Oil Cannabis Preparation for Pain in Parkinson's Disease [48]
4. Influence of CBD on Episodic Memory in Healthy Subjects (CoIL-Basel): Randomized Placebo Controlled Cross-over Study Investigating the Influence of CBD on Episodic Memory in Healthy Subjects [49]
5. Clinical Study Of caNNabidiol in childrEn and adolesCenTs with Fragile X (CONNECT-FX) (CONNECT-FX): This is a Randomized, Phase2 Phase 3, Double-Blind, Placebo-

Controlled Multiple-Center, Efficacy and Safety Study of ZYN002 Administered as a Transdermal Gel to Children and Adolescents with Fragile X Syndrome. [50]

Among those five August studies, not only neurological conditions are registered but also a cardiovascular condition is reported. This interventional clinical trial is intended to explore CBD in patients with heart failure in stages A-C American College of Cardiology/American Heart Association. The trial provides evidence that new areas are being contemplated. The study is within the initial clinical phases. The cardiovascular study is registered as a phase 1 trial, meaning that the study will focus mainly on the CBD safety. Since the goal of the study is to evaluate the safety, the primary outcome of the study is based on the incidence of events and serious adverse events that the participants exhibit when taking CBD.

Correspondingly, evaluating the remaining 2018 studies, there is substantial evidence that researchers are expanding the studies of CBD in fields other than the regular epilepsy and pain studies.

Arthritis is studied in the clinical trial: CBS Treatment in Hand Osteoarthritis and Psoriatic Arthritis. [51]

Infantile Spasms are studied in the clinical trial: A Study to Assess the Efficacy, Safety, and Tolerability of Cannabidiol Oral Solution with Vigabatrin as Initial Therapy in Participants with Infantile Spasms [52]

Genetic and rare disease-Prader-Willi Syndrome is studied in the clinical trial: A Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients with Prader-Willi Syndrome [53]

Crohn's Disease is studied in the clinical trial: Cannabidiol Usage as an Adjunct Therapy for Crohn's Disease [54]

Glioblastoma is studied in two clinical trials: TN-TC11G (THC+CBD) Combination with Temozolomide and Radiotherapy in Patients with Newly-diagnosed Glioblastoma [55] A Study of the Efficacy of Cannabidiol in Patients with Multiple Myeloma, Glioblastoma Multiform, and GI Malignancies [56]

Anxiety is studied in the clinical trial: Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot [57]

Hemodialysis is studied in the clinical trial (Impact of Cannabis Oil on Nutrition in Hemodialysis Patients Study (ICON-HP Study [58]

Autism is studied in the clinical trial: Shifting Brain Excitation-Inhibition Balance in Autism Spectrum Disorder [59]

There are an extensive number of trials that target several conditions with poor or without any prior and definitive safe and effective treatment. Those studies represent the new era of CBD clinical trials and denote the challenges that firms are willing to take. These consequences are valuable for the community in general because of the therapeutic options that will be available in the near future.

Challenges with the DEA imports and exports requirements

The U.S has confronted numerous drug trafficking concerns over the years, leading the agencies to opt for extreme measures to control the import and export of controlled substances within and from the United States. Currently, the DEA requires importers and exporters of

controlled substances to obtain an authorization prior to any imports into or from the United states. The Agency uses different mechanisms to regulate those imports and exports. Permits and declarations are among those that the Agency require. The administration uses mainly four forms:

1. DEA Form 161 to apply for a permit to export Controlled Substances,
2. DEA Form 236 to declare imports of Controlled Substances,
3. DEA Form 236 to declare exports of Controlled Substances,
4. DEA Form 357 to apply for a permit to import Controlled Substances for domestic and/or scientific purposes. [60, 61]

These DEA Forms are official requirements that, depending on the CSA schedule, stakeholders need to obtain prior to the execution of any international activities. When a firm wants to import or export a controlled substance from either Schedule I or Schedule II, they are required to have a permit (DEA- form 357 for imports and DEA-form 161 for exports). However, they are not required to fill out the declaration forms to import or export (DEA form 236) because a permit supersedes the declaration. In Table 6, the import and export requirements for each schedule are summarized. [61]

Table 6: DEA Imports and Exports Requirements Divided by Schedule

CSA Schedule	Form-161	Form 357	Form 236 Import	Form 236 Export
Schedule I	Required	Required	Not required	Not required
Schedule II	Required	Required	Not required	Not required
Schedule III Narcotic	Required	Required	Not required	Not required

CSA Schedule	Form-161	Form 357	Form 236 Import	Form 236 Export
Schedule III Nonnarcotic	Not required	Not required	Required	Required
Schedule III (delta-9-THC)	Required	Required	Not required	Not required
Schedule IV Narcotic	Required	Required	Not required	Not required
Schedule IV Nonnarcotic	Not Required	Not Required	Required	Required
Schedule V Narcotic	Not required	Required	Not required	Required
Schedule V Nonnarcotic	Not required	Not required	Required	Required

Under the Code of Federal Regulations, 21 CFR 1312.11, importers of Schedule I, Schedule II, Schedule III Narcotic, Schedule IV Narcotic and Schedule V Narcotic controlled substances are required to obtain a permit to import or Form 357. Even though Epidiolex (Cannabidiol) was classified in Schedule V, the federal register indicates that importers of certain FDA approved drugs containing CBD will require a permit (DEA Form 357). [60, 61] Permits to import are exclusive and are known to be very difficult to obtain. This is expected as the DEA is committed to protect the U.S from the entry of illegal substances.

Under 21 CFR 1312.21, exporters of Schedule I, Schedule II, Schedule III Narcotic and Schedule IV Narcotic controlled substances are required to obtain a permit to import or Form 161. Even though Epidiolex (Cannabidiol) was placed in the Schedule V category, and Schedule V drugs do not require a permit, the federal register indicates that exporters of certain FDA approved drugs containing CBD will require a permit (DEA Form 161). [60, 61]

Another regulatory change expected with the scheduling of Epidiolex (Cannabidiol) is concerning prescription refills. The current federal directives establish that Schedule III, Schedule IV and Schedule V controlled substances may be refilled if authorized by prescription. However, the prescription may only be refilled up to five times within six months after the date on which the prescription was issued.[62] Since Epidiolex is intended to be a prescription drug and it is a Schedule V drug, it will fall within this prescription condition. However, Cannabidiol is a Schedule I substance and its dispensing limits are limited to research use exclusively. In a near future, surveillance activities will possibly expose an irrational and indiscriminate use of Epidiolex (Cannabidiol) because of the current abuse status of THC. As a preventive action, the DEA should condition the prescription refills in the same they conditioned the import and export activities.

In conclusion, the DEA is creating new regulatory requirements for the specific kind of products in its intents to protect the U.S. from illicit drug trafficking and complying with international standards. It was unexpected that the DEA adopted the recommendation from the U.S. Department of Health and Human Services (HHS) and placed Epidiolex (Cannabidiol) in the Schedule V. The DEA had the option of placing the drug in Schedule II which automatically would have required importers or exporters to have a permit to perform that activities. The rational to reject that option is based on the facts provided in the recommendation of the HHS; they claim that since a Schedule II substance is considered to have a high abuse potential and Epidiolex

(Cannabidiol) has negligible abuse potential, the product should not be placed in Schedule II. It would be contradictory for the DEA to do so, that's why the easiest solution was to supplement the scheduling with extra regulatory requirements. The DEA is impacting the regulatory panorama by imposing the permit requirements. However, if GW Pharmaceuticals (the proprietary of Epidiolex) was conducting clinical trials and handling CBD, they must have already had a permit to import or export since CBD is a Schedule I within the CSA.

Epidiolex (Cannabidiol) NDA regulatory examination

The review of the NDA 210365 granted to GW Pharmaceuticals indicates that the firm is mandated to complete several regulatory requirements. The firm is required to perform post-marketing surveillance for liver toxicity after exposure to Epidiolex. This surveillance request is vital to fulfill the pharmacovigilance requirements and determine causality of the adverse events.[63]

Regarding pediatric regulatory requirements, since Epidiolex received an orphan drug designation, GW Pharmaceuticals is not required to provide an assessment of the safety and effectiveness of Epidiolex in pediatric patients. Nevertheless, the FDA granted a rare pediatric disease priority review voucher for which GW Pharmaceuticals is required to submit a report in 2023, as provided under section 529 of the Federal Food, Drugs and Cosmetic Act (FDCA).[63]

Regarding, the post-marketing regulatory requirements, the FDA determined that the analysis of spontaneous post-marketing adverse events reported by GW Pharmaceuticals under subsection 505(k)(1) of the Federal Food, Drugs and Cosmetic Act (FDCA) did not meet the requirements to assess a "known serious risk of liver injury" as required by section 505(o)(3) of the FDCA. Under section 505(o)(3) of the FDCA the FDA requires holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain

purposes. [64, 65] For the current NDA, the preclinical and clinical trials that GW Pharmaceuticals is required to conduct in order to fulfill the FDA requirements are depicted in Table 7. Also, the deadlines for completion have been included in the table.[65]

Table 7: Post-marketing studies required in the GW Pharmaceuticals NDA

Code	Studies	Study Completion by
3429-1	An embryofetal development study of 7-COOH-cannabidiol in rat.	December 2019
3429-2	A pre- and postnatal development study of 7-COOH-cannabidiol in rat.	December 2019
3429-3	A juvenile animal toxicology study of 7-COOH-cannabidiol in rat.	December 2019
3429-4	A 2-year carcinogenicity study of Cannabidiol in mouse	April 2020
3429-5	A 2-year carcinogenicity study of Cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat	August 2022
3429-6	Assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.	September 2019
3429-7	Assess the potential for chronic liver injury with Epidiolex, with evaluation including physical exam, serum/blood biomarkers, and other noninvasive measures of liver fibrosis, such as MRI or ultrasound-based elastography. Patients should be evaluated yearly for five years.	May 2027

Code	Studies	Study Completion by
3429-8	Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex (Cannabidiol) during pregnancy compared to an unexposed control population.	March 2027
3429-9	A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of caffeine in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."	June 2019
3429-10	A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2B6 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."	September 2019
3429-11	A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2C9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."	September 2019
3429-12	Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP2C19 inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.	September 2018
3429-13	Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP3A inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.	September 2018

Code	Studies	Study Completion by
3429-14	Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers.	August 2018
3429-15	A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGT1A9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."	September 2019
3429-16	A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGTB7 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."	September 2019
3429-17	A thorough QT trial at the maximum tolerable dose of Epidiolex that is feasible (e.g., dosing in the fed state), with appropriate controls (i.e., placebo and positive control).	July 2019

GW Pharmaceuticals represented that most of the risks associated with Cannabidiol appeared to be acceptable and that the only major risk is liver injury. GW Pharmaceuticals added that those potential risks can be appropriately handled with the inclusion of relevant language in labeling, education of health care professionals regarding the risk of transaminase elevation, the requirement of monitoring of liver enzyme levels and further characterization of the potential liver risks in the post-marketing studies.

At the present time, the two studies that evaluate drug-drug interactions to determine the effects of a strong CYP2C19 inhibitor and CYP3A inhibitor on the pharmacokinetics of Epidiolex

in healthy volunteers have been successfully submitted and added to the New Drug Application file. The studies concluded that there were no increases in valproic acid, stiripentol or clobazam levels. But there was an active metabolite of clobazam (n-desmethylclobazam) that did show an unexpected result. The evaluation of the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers has been completed and added to the NDA. Even though the data and conclusions from the study are not available, rifampin is a CYP3A4 inducer that has been reported to reduce CBD levels by 50 percent to 60 percent.[66]

Studies from 3429-1 to 3429-6 are part of the pre-clinical studies that the firm need to achieve in order to be in compliance with the FDA requirements. The remaining studies are focused on clinical outcomes using human subjects. The goal is to confer robustness of the claims raised by GW Pharmaceuticals, and because of the nature of the studies, longer completion deadlines have been given.

To conclude, in the current year 2018, the number of clinical trials has grown significantly (18.44%) and, with this increase, a substantial expansion of the therapeutic areas studied using CBD. Also, the regulatory burden for imports and exports has increased for those firms that do not possess a permit due to the conditional scheduling Epidiolex purports. The NDA approval was a great step from the FDA in regards to the scientific tendency in evaluating new therapies. However, GW Pharmaceuticals is expected to conduct those studies to remain in compliance with the FDA NDA requirements.

CHAPTER V

ECONOMIC AND MARKETING EVALUATION

Multiple factors are included in the cost of a drug that enters to the market. Wet-chemistry testing, pre-clinical trials, clinical trials, manufacturing, marketing etc. are some of those factors. Transforming and escalating a drug from a lab to the industrial production is not an easy task. It entails several tangible and intangible costs that are translated into the final value of the product. Presently, twice as much is spent on manufacturing as opposed to research and development.[67]

In 2001, the manufacturing cost was approximately $90 billion for the top 16 pharmaceutical companies [67, 68] The expenses in manufacturing are known as cost of goods sold. Those costs are associated with the manufacturing process of a product that a company sells during a certain period. Thus, the only costs included in the calculations are the costs directly associated to the production of the products, such as the cost of labor, materials, and manufacturing overhead.[69]

In 2017, the USA hemp-derived CBD products reached a total sales record of $190,000,000 of U.S dollars. In 2017, the total sales of hemp-base products reached $820,000,000 US dollars. The hemp-based products industry is very diverse and versatile, in terms of the economic results, Figure 12 represents the sales in 2017 (in USD)[70] for some subcategory of products. The estimates for sales of all hemp derived products is $1 billion US dollars for 2018 and $1.9 billion US dollars in 2019.[70]

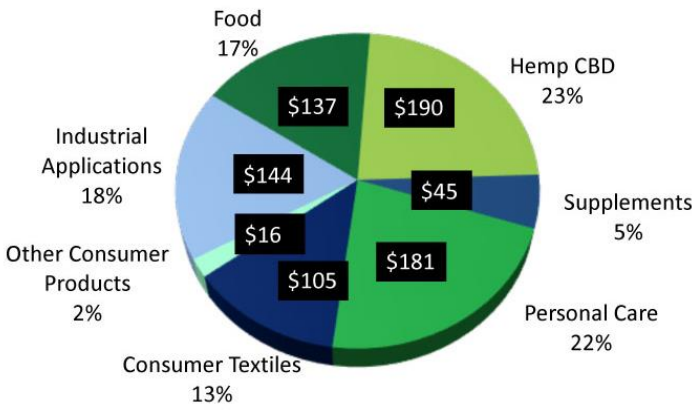

Figure 12: US. Hemp-based product sales by category in 2017

GW Pharmaceutical estimates the price of Epidiolex at $32,500 U.S. dollars per year, depending on the dosing and weight of the patient. [71] According to the company's North America branch, out-of-pocket costs for patients taking Epidiolex could range from $5 to $10 dollars a month for those in state Medicaid programs. For those patients that have private insurance the cost is estimated to be around $200 dollars. [72, 73]

Market price and cost-therapy evaluation

The following calculations and estimates are based on the information available on the GW Pharmaceutical's website, news articles, and scientific bibliography. The formulation of Epidiolex is presented as an oral solution 100 mg/mL in a 100 mL vial.

Assuming that patient XT weights 30 kg, one-year of therapy would be:

- Starting dose: 2.5 mg/kg taken twice daily (5 mg/kg/day)

For patient XT, a starting dose of 150 mg/day

Patient XT would need to take 1.5 mL/day (0.75 mL twice daily) from the 100 mL vial.

After one week: each dose will be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg/day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). Depending on the individual clinical response and tolerability the final therapeutic dose will be 10 mg/kg twice daily (20 mg/kg/day).

- Therapeutic dose: 10 mg/kg taken twice daily (20 mg/kg/day)

For patient XT a therapeutic dose of 600 mg/day

Patient XT would need to take 12 mL/day (6 mL twice daily) from the 100 mL vial

In conclusion, a 30 Kg patient will consume 1 vial every 8 days, (at the maximum therapeutic dose). Patient XT will use 4 vials a month, and 48 vials a year. GW Pharmaceuticals estimates that on average therapy would cost $32.500 USD, (daily cost of $89 dollars). The estimate for a price per 100 mL vial (based on this assumptions) would be approximately $667 dollars.

The cost-comparison study 'Stiripentol (Diacomit), For Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)'[74], reports the annual cost for a 30 kg patient with Dravet Syndrome. One of the therapies is based on a combination of stiripentol and clobazam. The yearly cost of a treatment with stiripentol is $13,943 and a yearly cost of clobazam is $58.40. The total yearly therapy cost using both drugs is $14,001. The costs are indicated in Canadian Dollars. In order to compare the numbers, the values are converted to USD: 1 Canadian Dollar equals 0.76 USD.

Table 8: Dravet therapy cost comparison versus Epidiolex (Cannabidiol) therapy

Therapy	Annual Cost (USD)	Daily Cost (USD)
Epidiolex (Cannabidiol)	$32,500	$89.00
Diacomit (Stiripentol)+Clobazam	$10,640	$29.15
Difference	$21,860	$59.85

The treatment for a 30 kg patient with Dravet syndrome would be significantly more expensive with Epidiolex (Cannabidiol) than with the Diacomit (Stiripentol)+Clobazam therapy as depicted in Table 8. The therapy cost with Epidiolex (Cannabidiol) increases almost 205% when compared to Diacomit (Stiripentol)+Clobazam. However, as mentioned in literature and the reasoning as to why Epidiolex got FDA approval, Epidiolex has been proven to be safe and effective for the treatment of seizures associated with these two rare and severe forms of epilepsy (Dravet syndrome and Lennox-Gastaut syndrome).

Evaluation of Marketing and FDA thinking

On June 25, 2018 after the marketing approval of Epidiolex, the FDA commissioner, in a press announcement, expressed the FDA's thinking in regards to Epidiolex and the commitment of the Agency to the research of marijuana-derived treatments. Commissioner Gottlieb stated that [28,84] "This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies. And, the FDA is committed to this kind of careful scientific research and drug development." In addition, the commissioner referred to the systematic initiatives by pointing out that "Controlled

clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA's drug approval process, is the most appropriate way to bring marijuana-derived treatments to patients. (…). We'll continue to support rigorous scientific research on the potential medical uses of marijuana-derived products and work with product developers who are interested in bringing patients safe and effective, high quality products. But, at the same time, we are prepared to take action when we see the illegal marketing of CBD-containing products with serious, unproven medical claims. Marketing unapproved products, with uncertain dosages and formulations can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases." [28,84] The Agencies' willingness to explore new areas of therapeutics seems to be more comprehensive over the time. This controversial approval defied the thinking that was associated to marijuana only as a recreational substance. For many years the medical value of marijuana was subjected to public scrutiny and governmental preconception. However, today the properties of marijuana and its purified components (CBD and THC) are being highly explored.

The status of marijuana was not the same in 1970. The DEA included marijuana under the Schedule I classification for the first time under the Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act of 1970)[75], due to the high potential for abuse that was experienced during those years. It was not simply the potential for abuse that was the reason of the scheduling, but also the lack of accepted safety for use under medical supervision and the fact that there was not any accepted medical use. In 1995, Dr. Jon Gettman submitted a request to the DEA for the rescheduling of marijuana and other cannabinoids. Three years later, in 1998, the DEA requested for HHS to provide pertinent medical and scientific determination to schedule marijuana. In 2001, as a result of the HHS evaluation, the DEA denied the request to reschedule marijuana.[76]

The fact that previously the DEA took three years to conduct the rulemaking proceedings is an irrefutable confirmation that the regulatory panorama has changed. The current Schedule V for Epidiolex (Cannabidiol) published in the Federal Register on September 28, 2018, took no longer than three months.[32] There are possible assumptions that could be used to explain the reasoning of this expedited review and scheduling process. Perhaps, the HHS findings and advice are the main reason. The concept concluded that Epidiolex formulation had a very low potential for abuse. Since the potential for abuse is one of the major points in the eight factor analysis, the decision to place the drug in Schedule V could be taken with any doubt. Certainly, the decision was established on the grounds that Schedule V is the lowest abuse potential category.

Nevertheless, the scheduling determination for marijuana hasn't changed over the years. On April 2001, the response of the HHS recommended that marijuana was to remain a Schedule I drug.[76] The decision was made because three out of five parameters that the FDA uses to determine whether a substance has a "currently accepted medical use" were not met. According to 57 FR 10499, 10504-06, the five criteria that enable a product to have a current medical use are: (1) The drug's chemistry is known and reproducible; (2) There are adequate safety studies; (3) There are adequate and well-controlled studies proving efficacy; (4) The drug is accepted by qualified experts; and (5) the scientific evidence is widely available. [77] The Agency recognized that items 2 and 5 were in rule and met the definition at the time of the request. However, they found that items 1, 4 and 5 did not meet the definition and criteria. Although, item 4 was not satisfied, it was an inconclusive outcome only because a consensus among the experts was not achieved. The report argued that a complete scientific analysis of all the chemical components found in marijuana had not been conducted and that there were no studies that had assessed the efficacy of marijuana for any medical condition. Based on that evidence, the DEA had the right to deny the rescheduling

request. On October 2002 [78] and December 2009 [79], individuals from the community petitioned similar rescheduling requests to the DEA. The final determination for both requests was a denial. Although, new evidence and studies were provided, the DEA reached the same conclusion as in Dr. Gettmann's request. Again, the Agency upheld its thinking by finding that marijuana has no currently accepted medical use, marijuana has a high potential for abuse and marijuana lacks accepted safety for use under medical supervision. In the provisions of the last statement, the Agency contended that at the time of the request there were no FDA approved marijuana products, nor was marijuana under a NDA evaluation.

In light of the new evidence provided by GW Pharmaceutical to support the Epidiolex (Cannabidiol) NDA approval and DEA CSA scheduling, the perspective for other active ingredients of marijuana could possibly change. The DEA and FDA position regarding the use of active ingredients of marijuana products is currently favorable, and stakeholders should take advantage of this to petition for a new request for evaluation. The following concepts could be part of the supporting evidence for a new request:

1. The argument that the DEA used to deny the request is that marijuana lacks acceptable safety for use under medical supervision and claimed that not studies were reported. At the present time, the NIH U.S National Library of Medicine Clinical trials website reports clinical studies using cannabis. The study of the safety and efficacy of medical cannabis oil in the treatment of patients with chronic pain registered in November, 2017 [80] is probably the most appropriate to contest the Agency claims. Since that study will assess the efficacy of marijuana for patients with chronic pain, it should substantiate and address those requirements. Additionally, now that Cannabidiol will be available as a prescription formulation, there will be evidence of safety under medical supervision for one of the active

ingredients of marijuana. Recently, in Europe and Asia studies with Sativex (CBD and THC) have been successfully carried out and would be also an important provision to backup this request. [77]

2. Characteristically, marijuana and the formulation of Epidiolex are two different products. However, the approved NDA's evidence can be used in marijuana's favor to substantiate the drug's chemistry reproducibility and identity, criteria required to stablish the currently medical use status. Additionally, to support this item, in 2016 the FDA published the guidance Botanical Drug Development[83] as a way to assure quality in the manufacturing of botanicals like marijuana. The guidance is an excellent source to ensure compliance with the chemistry, manufacturing and controls sections.
3. The drug abuse concept is still difficult to counter-argue. However, it could be established that marijuana's abuse potential is not high enough as to be classified within the Schedule I. The National Institute on Drug Abuse suggests that 9 percent of people that consume marijuana will become dependent on it. [81] Thus, the numbers are not as critical as heroin (Schedule I) and cocaine (Schedule II) [82], and therefore the classification can be rescheduled on the grounds of that concept.

This thesis serves as an overview for the regulatory community to explicitly outline the existing changes and possible future modifications of regulatory and enforcement activities by FDA and DEA. In addition, it provides a summary of new conditions and diseases being explored in clinical trials using CBD.

It is recommended that the potential number of prescriptions (such as off-label indications) and new subgroups (such as new indications) are taken into consideration when concluding that Epidiolex's approval will significantly impact the enforcement of DUI's.

It is recommended that official agencies disseminate information to the public discerning the approval and scheduling of Epidiolex and current illegal status of CBD as a schedule I substance.

The advertisement of products containing CBD (Dietary supplements, food and beverages etc.) is increasing considerably after the Epidiolex approval. It is suggested that both agencies prepare and launch new mechanisms to safeguard the market form the incursion of misleading products.

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APPENDIX I

Clinical Trials Summary Classified by Month

January 2018

Title:	Evaluation of the Effects of Cannabidiol (CBD) Compared to Delta-9-Tetrahydrocannabinol (THC) and Alprazolam
Status:	Completed
Study Results:	No Results Available
Interventions:	Drug: THC|Drug: Alprazolam|Drug: Placebo oral capsule|Drug: CBD
Start Date:	December 4, 2017
First Posted:	January 12, 2018
Last Update Posted:	June 14, 2018
Locations:	Debra Kelsh, MD, Overland Park, Kansas, United States
URL:	https://ClinicalTrials.gov/show/NCT03398083

February 2018

Title:	A Study to Assess the Efficacy, Safety, and Tolerability of Cannabidiol Oral Solution With Vigabatrin as Initial Therapy in Participants With Infantile Spasms
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol Oral Solution|Drug: Placebo|Drug: Vigabatrin
Start Date:	September 5, 2018
First Posted:	February 5, 2018
Last Update Posted:	October 12, 2018
Locations:	Nicklaus Children's Hospital, Miami, Florida, United States|Beaumont Children's Hospital, Royal Oak, Michigan, United States|Oregon Health & Science University, Portland, Oregon, United States|Institute for Research and Innovation MultiCare Health System, Tacoma, Washington, United States
URL:	https://ClinicalTrials.gov/show/NCT03421496

March 2018

Title:	A Study to Assess the Long-Term Safety of Pharmaceutical Grade Synthetic Cannabidiol Oral Solution in Patients With Prader-Willi Syndrome
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol Oral Solution

Start Date:	September 6, 2018
First Posted:	March 8, 2018
Last Update Posted:	October 12, 2018
Locations:	Institute for Research and Innovation MultiCare Health System, Tacoma, Washington, United States
URL:	https://ClinicalTrials.gov/show/NCT03458416

Title:	Cannabidiol - an in Vivo Innovative Drug Delivery Study
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol
Start Date:	January 15, 2019
First Posted:	March 20, 2018
Last Update Posted:	August 31, 2018
Locations:	Department I of Pharmacology, University of Cologne, Cologne, Germany
URL:	https://ClinicalTrials.gov/show/NCT03471559

Title:	Cannabidiol Usage as an Adjunct Therapy for Crohn's Disease
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol|Drug: Placebo oral capsule
Start Date:	July 2018
First Posted:	March 16, 2018
Last Update Posted:	March 20, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03467620

Title:	A Study to Assess the Safety and Tolerability of ZX008 in Children and Young Adults With DS or LGS Currently Taking CBD
Status:	Active, not recruiting
Study Results:	No Results Available
Interventions:	Drug: ZX008 02 and 0.8 mg/kg/day
Start Date:	January 19, 2018
First Posted:	March 15, 2018
Last Update Posted:	August 14, 2018
Locations:	PANDA Neurology/CIRCA, Atlanta, Georgia, United States|MultiCare Institute for Research & Innovation, Tacoma, Washington, United States
URL:	https://ClinicalTrials.gov/show/NCT03467113

April: Zero Studies

May 2018

Title:	Cannabidiol and Prolonged Exposure
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Behavioral: Prolonged Exposure|Drug: Cannabidiol|Drug: placebo
Start Date:	November 1, 2018
First Posted:	May 8, 2018
Last Update Posted:	September 28, 2018
Locations:	VA San Diego Healthcare System, San Diego, CA, San Diego, California, United States
URL:	https://ClinicalTrials.gov/show/NCT03518801

Title:	Shifting Brain Excitation-Inhibition Balance in Autism Spectrum Disorder
Status:	Active, not recruiting
Study Results:	No Results Available
Interventions:	Drug: PLC|Drug: CBD|Drug: CBDV
Start Date:	August 22, 2016
First Posted:	May 25, 2018
Last Update Posted:	May 25, 2018
Locations:	King's College London, London, United Kingdom
URL:	https://ClinicalTrials.gov/show/NCT03537950

Title:	Pain Research: Innovative Strategies With Marijuana
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabis Edible
Start Date:	June 1, 2018
First Posted:	May 11, 2018
Last Update Posted:	October 10, 2018
Locations:	Center for Innovation and Creativity, Boulder, Colorado, United States
URL:	https://ClinicalTrials.gov/show/NCT03522324

Title:	TN-TC11G (THC+CBD) Combination With Temozolomide and Radiotherapy in Patients With Newly-diagnosed Glioblastoma
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: TN-TC11G|Drug: Temozolomide Oral Product|Radiation: Radiotherapy
Start Date:	June 2018
First Posted:	May 18, 2018
Last Update Posted:	May 22, 2018

Locations:	Institut Català d'Oncología L'Hospitalet, L'Hospitalet de Llobregat, Barcelona, Spain|Hospital Universitario Son Espases, Palma de Mallorca, Mallorca, Spain|Consorcio Hospitalario Provincial de Castellón, Castelló, Valencia, Spain|Hospital del Mar, Barcelona, Spain|Complejo Hospitalario Regional Virgen de las Nieves, Granada, Spain|Hospital Universitario 12 de Octubre, Madrid, Spain|Hospital Regional Universitario de Malaga, Malaga, Spain|Hospital Clínico Universitario de Salamanca, Salamanca, Spain
URL:	https://ClinicalTrials.gov/show/NCT03529448

June 2018

Title:	Cannabidiol for the Treatment of Anxiety Disorders: An 8-Week Pilot Study
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol (CBD) Oil Capsules|Drug: Sunflower Lecithin Oil in Capsule
Start Date:	August 2018
First Posted:	June 8, 2018
Last Update Posted:	June 8, 2018
Locations:	MacAnxiety Research Centre, Hamilton, Ontario, Canada
URL:	https://ClinicalTrials.gov/show/NCT03549819

Title:	Cannabinoids in PLWHIV on Effective ART
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Low CBD dose TN-CT11LM oral capsules(THC2.5 mg/CBD2.5 mg)|Drug: High CBD dose TN-TC19LM oral capsules (THC 5 mg / CBD 45 mg)
Start Date:	August 2018
First Posted:	June 8, 2018
Last Update Posted:	June 8, 2018
Locations:	Chronic Viral Illnesses Service, McGill University Health Centre—Glen Site, Montreal, Quebec, Canada
URL:	https://ClinicalTrials.gov/show/NCT03550352

Title:	Inhaled Cannabis Versus Fentanyl Buccal Tablets for Management of Breakthrough Pain in Cancer Patients
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Combination Product: PPP001|Drug: FBT|Combination Product: Active PPP001 with FBT Placebo|Drug: Active FBT with PPP001 Placebo
Start Date:	September 1, 2018
First Posted:	June 21, 2018
Last Update Posted:	June 25, 2018

Locations:	Sante Cannabis, Montréal, Quebec, Canada
URL:	https://ClinicalTrials.gov/show/NCT03564548

July 2018

Title:	A Study of Tolerability and Efficacy of Cannabidiol on Motor Symptoms in Parkinson's Disease
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol|Other: Placebo
Start Date:	December 2018
First Posted:	July 10, 2018
Last Update Posted:	October 16, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03582137

Title:	A Study of the Efficacy of Cannabidiol in Patients With Multiple Myeloma, Glioblastoma Multiforme, and GI Malignancies
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol|Drug: Bortezomib|Drug: Leucovorin|Drug: 5-FU|Drug: Oxaliplatin|Drug: Bevacizumab|Drug: Irinotecan|Drug: Gemcitabine|Drug: Temozolomide
Start Date:	January 15, 2019
First Posted:	July 31, 2018
Last Update Posted:	July 31, 2018
Locations:	Southwest Cancer Center, Orlando, Florida, United States
URL:	https://ClinicalTrials.gov/show/NCT03607643

Title:	Cannabis and Thought Disorder in Schizophrenia
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Other: Cannabis and thought disorder in schizophrenia:clinical and neuroimaging relationships
Start Date:	October 2, 2018
First Posted:	July 31, 2018
Last Update Posted:	September 27, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03608137

August 2018

Title:	Cannabidiol in Patients With Heart Failure Failure in AHA/ACC Stages A-C
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol
Start Date:	March 1, 2019
First Posted:	August 16, 2018
Last Update Posted:	August 16, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03634189

Title:	Cannabis Oil for Chronic Non-Cancer Pain Treatment
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: CBD|Drug: CBD+THC|Other: Placebo
Start Date:	October 1, 2018
First Posted:	August 17, 2018
Last Update Posted:	August 27, 2018
Locations:	Michael G. DeGroote Pain Clinic, Hamilton, Ontario, Canada|Toronto Poly Clinic, Toronto, Ontario, Canada
URL:	https://ClinicalTrials.gov/show/NCT03635593

Title:	Cannabis Oil for Pain in Parkinson's Disease
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabis Oil
Start Date:	December 2018
First Posted:	August 20, 2018
Last Update Posted:	August 20, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03639064

Title:	Influence of CBD on Episodic Memory in Healthy Subjects
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Drug: Verum|Drug: Placebo
Start Date:	August 13, 2018
First Posted:	August 13, 2018
Last Update Posted:	October 11, 2018
Locations:	University of Basel, Division of Cognitive Neuroscience, Basel, Switzerland

URL:	https://ClinicalTrials.gov/show/NCT03627117

Title:	Clinical Study Of caNNabidiol in childrEn and adolesCenTs With Fragile X (CONNECT-FX)
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Drug: ZYN002 - CBD Transdermal Gel|Other: Placebo Transdermal Gel
Start Date:	June 12, 2018
First Posted:	August 3, 2018
Last Update Posted:	October 18, 2018

Title:	Cannabidiol for Drug Resistant Pediatric Epilepsy (Expanded Access Use)
Status:	Available
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol
Start Date:	null
First Posted:	September 18, 2018
Last Update Posted:	September 18, 2018
Locations:	University of Mississippi Medical Center, Jackson, Mississippi, United States
URL:	https://ClinicalTrials.gov/show/NCT03676049

Title:	Impact of Cannabis Oil on Nutrition in Hemodialysis Patients Study (ICON-HP Study)
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabis oil|Drug: Placebo/ Regular Oil
Start Date:	September 15, 2018
First Posted:	September 10, 2018
Last Update Posted:	September 11, 2018
Locations:	Asaf ha Rofeh, MC, Zrifin, Israel
URL:	https://ClinicalTrials.gov/show/NCT03664141

Title:	Effects of Cannabis on Prescription Drug Abuse Liability and Analgesia
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Oxycodone|Drug: Cannabis (THC:CBD = ~ 1:0)|Drug: Cannabis (THC:CBD = ~ 0:1)|Drug: Cannabis (THC:CBD = ~ 1:1)|Drug: Placebo
Start Date:	October 1, 2018
First Posted:	September 21, 2018

Last Update Posted:	September 21, 2018
Locations:	
URL:	https://ClinicalTrials.gov/show/NCT03679949

October 2018

Title:	CBS Treatment in Hand Osteoarthritis and Psoriatic Arthritis.
Status:	Not yet recruiting
Study Results:	No Results Available
Interventions:	Drug: Cannabidiol|Drug: Placebo Oral Tablet
Start Date:	October 20, 2018
First Posted:	October 3, 2018
Last Update Posted:	October 8, 2018
Locations:	N/A
URL:	https://ClinicalTrials.gov/show/NCT03693833

Title:	Medical Cannabis Registry and Pharmacology
Status:	Recruiting
Study Results:	No Results Available
Interventions:	Behavioral: Multiple questionnaires administered
Start Date:	July 15, 2018
First Posted:	October 8, 2018
Last Update Posted:	October 8, 2018
Locations:	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States
URL:	https://ClinicalTrials.gov/show/NCT03699527