Whitepaper

Digamma Consulting

The Federal Recreational Hemp Phenomenon

By Marco Troiani

The purpose of this document is to outline the draft of the federal recreational hemp phenomenon, including each sub-section. The document itself begins in the first section, but this paragraph is intended as an orienting text to help guide a reader through the draft and its component sections with ease.

EMERALD SCIENTIFIC

HISTORY

Many people know cannabis as an illicit and popular recreational drug from their youth. As many young people are prone to questioning established traditions, the contrast between the legality, and social harm, of alcohol and the illegality of cannabis may have raised some eyebrows. Alcohol was legal but was associated with violence and anti-social behavior, but cannabis was associated with peaceful hippies and dropouts. Additionally, the toxicity of alcohol, especially over a long period of time, was starting to be known to the general public, and evidence was starting to show that cannabis lacked the highly toxic profile of alcohol. At the close of the 20th century, many were thinking that the legalization of cannabis was a phenomenon to be experienced in their lifetime.

Starting at the end of the 20th century, cannabis began being decriminalized and legalized by U.S. state governments, starting with medical cannabis in California in 1996 thanks to the Dennis Peron-driven proposition 215, which was borne out of the HIV/AIDS crisis in the gay community, primarily centered on San Francisco's Castro neighborhood. Since those days in 1980s, a large amount of peer-reviewed medical science papers have come out showing that cannabinoids and terpenoids present in cannabis helped to treat AIDS symptoms, such as AIDS-associated wasting syndrome. This effectiveness was so astounding during the medical crisis caused by HIV/AIDS that, even with a federal prohibition on cannabis, a THC pharmaceutical formulation was approved by the FDA for HIV/AIDS wasting syndrome and it was marketed under the name Marinol, with the generic name Dronabinol.

After California had established that medical cannabis programs initiated by state legislation chambers were possible, more states began to follow in the legalization process. Although federal officers continued to enforce federal cannabis prohibition on operators that were legal in the eyes of the state of California, state authority to legalize cannabis for medical purposes had been established. In 2012, both Colorado and Washington passed recreational adult-use bills that lifted the medical necessity as a prerequisite to cannabis consumption.

The introduction of recreational (sometimes called adult-use) bills expanded the profitability of cannabis significantly. At the time, California's medical program was only allowing medically relevant exceptions to federal laws, which only affect a small portion of the population. Even within this population, only a minority of eligible patients would use cannabis, as many were wary of the illicit association. The Colorado and Washington recreational bills demonstrated to the United States generally that a lucrative market was possible in nearly every U.S. state. In the years after 2012, some financial thinkers in the U.S. were stating that the national legalization and taxation of cannabis would be capable of balancing the debt on the federal or state budget.

As various waves of legalization worked through various states at the medical and recreational level, the so-called green wave seemed to be in full effect. As of April 2023, 22 states, two territories, and Washington, DC all had some form of cannabis legalization. Dispensaries open to anyone aged 21 and over, previously a phenomenon associated with Denver, CO, can now be seen all over the west coast, in about half of the east coast states, and also in mid-western states like Michigan and Missouri.

But as more states initiated cannabis programs, the federal prohibition on cannabis remained on the books, if not fully enforced. After 2013, U.S. Deputy Attorney General James M. Cole issued the Cole Memorandum, instructing federal prosecutors not to use federal resources to enforce federal cannabis prohibition in a state where it had been legalized by the state government. This brought an end to the threat of federal agents taking action against state-licensed cannabis operators, but many of the federal restrictions still prevented the cannabis industry from growing organically. All interstate commerce is prohibited for the cannabis industry as that is well defined as federal jurisdiction. This has created an economic landscape where cannabis operators re-apply as a new entity in new jurisdictions rather than simply directly expanding as traditional business would. Financial and tax issues surrounding the 280E clause that prevents cannabis business from writing off the Cost of Goods Sold (COGS) when those goods are Schedule I substances also severely limits the profitability of state-licensed cannabis business when compared to similar industries.

As the legal cannabis market seemed to stabilize leading up to 2018, a new phenomenon started appearing in the U.S. CBD products were being sold not only in state-licensed dispensaries but were showing up in nearly every corner smoke

shop in the country, regardless of whether that state had passed a cannabis reform bill or not. These CBD products were not produced from state-licensed cannabis but from federally legal hemp. These products were being distributed to low cost and ubiquitous vendors all over the country and without taking the 280E tax penalty that state-licensed operators were bound to. There seemed to be a federal loophole for cannabinoids derived from hemp to bypass the ills of the state-licensed operators, but it appeared to only apply to the non-psychoactive compound CBD.

As this federal cannabinoid loophole became more well known, psychoactive cannabinoids started appearing in smoke shops all over the country as well. Delta-8-THC and hexahydrocannabinol (HHC) are two of the more popular examples sold as edibles and vape pens in many smoke shops. When the federal hemp law that was originally designed for industrial hemp started applying to medically relevant cannabinoids like CBD, it seemed a reasonable state of affairs due to CBD's non-psychoactive status and low potential for abuse. CBD from hemp seemed more similar to a vitamin or supplement taken for a consumer's wellbeing than a recreational drug. But when the psychoactive cannabinoids began to appear on a less regulated market, a different landscape emerged. What many state-licensed operators that produce completely natural psychoactive cannabis are finding is that they are in unfair competition with recreational hemp operators. Some consumers are starting to prefer these more common and reliable brands that are present all over the country over the patchwork of competing state-level operators that run local dispensaries.

At this time, the recreational cannabinoid market seems to be upside down thanks to the explosion of the recreational hemp phenomenon. To better understand this phenomenon and the practical consequences of it for the industry, the technical aspects have been organized into the three categories of chemistry: law, analysis, and a brief conclusion. Because different readers have different areas of expertise and in-depth knowledge, the division is designed to assist each reader in finding the most relevant and helpful information.

CHEMISTRY

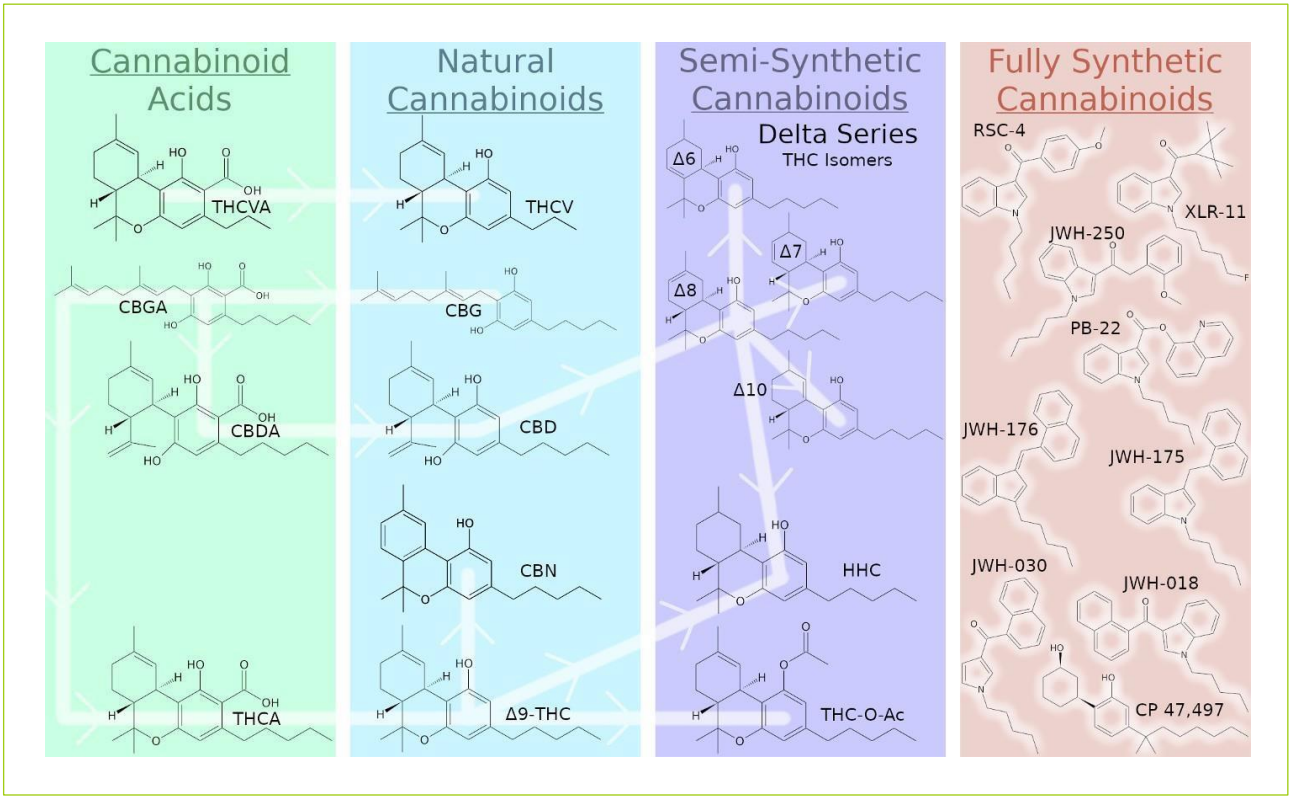
To properly understand the history, law, and future opportunities relating to cannabinoid compounds, familiarity with the chemistry of these compounds is critical. A scope has been presented here that is deep enough for a professional chemist, but broad and clear enough to be helpful to non-scientists to whom this information has relevant consequences.

Cannabinoid chemistry can appear both complex in nature and vast in scope, so an illustrative diagram outlining the chemistry has been created in Imageα below. The image has four parallel columns categorizing cannabinoid compounds from left-to-right: natural cannabinoid acids, natural cannabinoid neutrals, semi-synthetic cannabinoids, and fully synthetic cannabinoids.

Cannabinoid acids are the compounds produced by the cannabis plant. These organic acids are generally precursors to the more familiar cannabinoids included in the next section, natural cannabinoids, such as THC and CBD. Their acid forms, THCA and CBDA, respectively, are the compounds actually produced by the plant itself.

Natural cannabinoid neutrals are created from cannabinoid acids by natural physical processes. Most involve decarboxylation, a process that converts acids to their free cannabinoid forms, releasing carbon dioxide (such as THCA → THC or CBDA →CBD). This process happens spontaneously at the high temperatures associated with smoking and baking, and much more slowly at room temperature in the presence of excess light.

Semi-synthetic cannabinoids are those that are synthesized from natural cannabinoids through a man-made chemical reaction. These can include



Imageα – An illustrative diagram showing the chemical structure of the four major classes of cannabinoids: cannabinoid acids (green), natural cannabinoids (blue), semi-synthetic cannabinoids (purple), and fully synthetic cannabinoids (red). The sources of each molecule are related to other molecules in the diagram through white arrows indicating a chemical reaction. Image credit: Digamma.

compounds such as THC-O-Acetate, HHC, and the delta series of THC isomers, such as delta-8-THC.

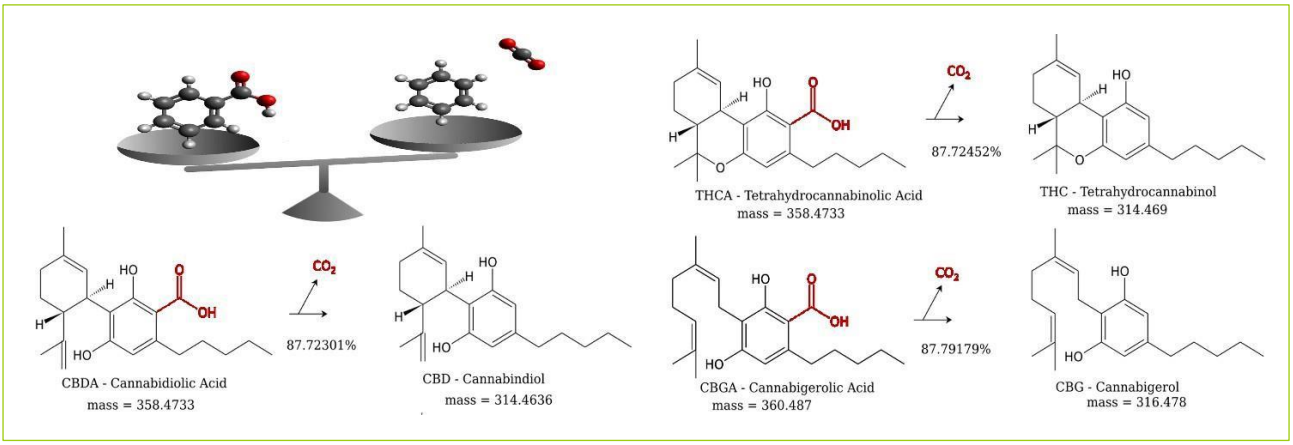
Fully synthetic cannabinoids are compounds that are synthesized in a laboratory by precursor chemicals that bear little structural similarity to natural cannabinoids but are known to activate biochemical cannabinoid receptors. The term phytocannabinoid (meaning from a plant source) is used to distinguish from both synthetic cannabinoids and animal-derived endocannabinoids such as anandamide.

To help illustrate the transitions from cannabinoid acid to free cannabinoid, we have reproduced a decarboxylation diagram in Image**β**. The top-left image shows how the loss of the carboxyl group as CO^2 leaves less mass of substance after decarboxylation, a loss that can affect the final yield calculations of any end product. The remaining quadrants show the exact mass loss for the three most common cannabinoid acids: THCA, CBGA, and CBDA. To help make these mass losses more intuitive, we have displayed the remaining mass, after decarboxylation, as a percentage of the original mass, for each cannabinoid decarboxylation reaction.

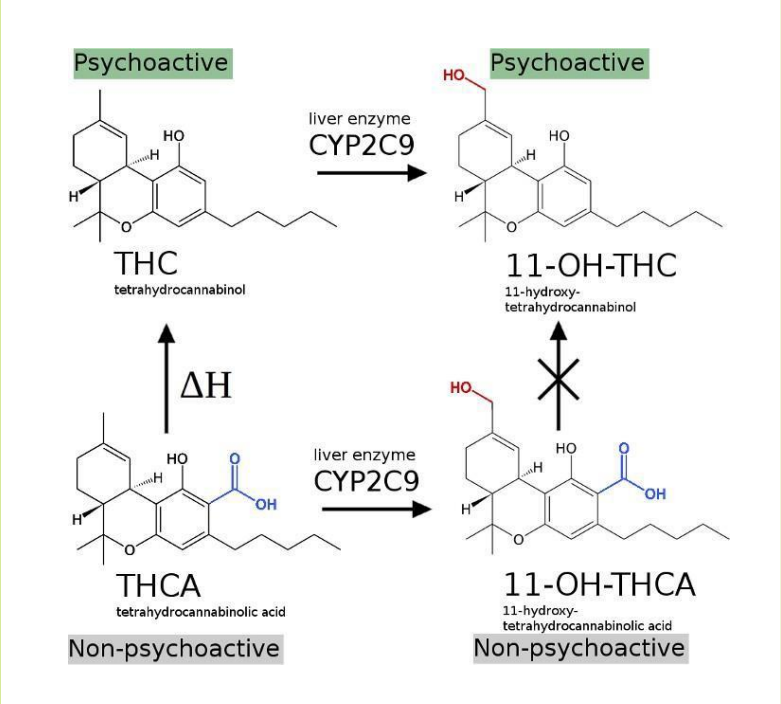
There are medically relevant differences between cannabinoids and cannabinoid acids, too. Until recently, many cannabis producers incorrectly assumed that because THCA converts to THC so readily outside the human body that ingested THCA would become THC in the human body. What experiments have shown is that once THCA enters the human body it will not convert to THC or its metabolites in any appreciable amount. Interestingly, both THCA and THC are metabolized by the same liver enzyme (CYP2C9), but inter-conversion after ingestion is not believed possible at this time. The lack of inter-conversion has particularly salient consequences when one considers that THCA isomers tend to be non-psychoactive whereas THC isomers tend to be psychoactive in humans. We have illustrated this phenomenon in Image**γ**.

To cover the remaining chemical phenomenon that are relevant to understanding the recreational hemp phenomenon, it may be helpful to look back to the year 2014. At this point in time, Colorado has recreational cannabis, but California, Maine, Massachusetts, and Nevada still have medical cannabis programs that are poised to expand to recreational in all four states in November 2016; the 2018 Farm Bill was still years away, and CBD was being treated as a non-psychoactive unregulated supplement with a high cost.

In 2014, many farmers were looking at hemp as a new opportunity to sell unscheduled drugs such



Imageβ – An image showing the concept of decarboxylation with an emphasis on cannabinoids. Clockwise from top-left: an illustration of how the loss of a carboxylic acid through decarboxylation causes a loss of mass (weight), a skeletal diagram showing the exact mass of decarboxylation of THCA>THC, a skeletal diagram showing the exact mass of decarboxylation of CBGA>CBG, a skeletal diagram showing the exact mass of decarboxylation of CBDA>CBD. Image credit: Digamma.

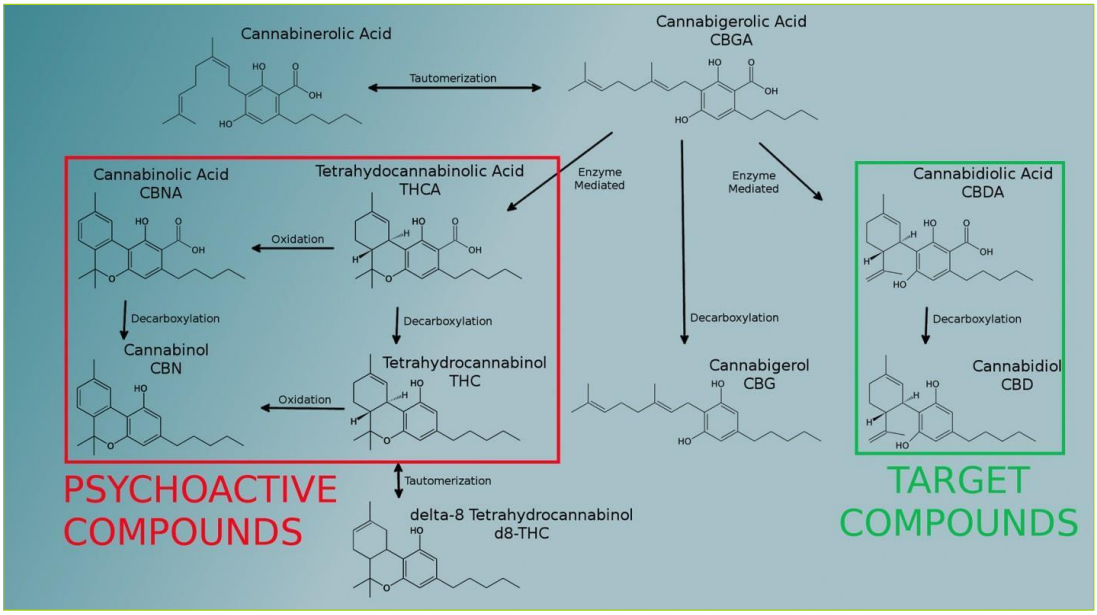


Imageγ – A diagram outlining the biochemically and medically relevant aspects of cannabinoid v. cannabinoid acid metabolism. The precursor THCA is present in the bottom-left of the image, showing the heat mediated decarboxylation creating THC in the top-left. Both THCA and THC are metabolized by CYP2C9 (liver enzyme) to create the 11-OH metabolites of both components. The psycho-activity of each of these components and their natural human metabolites is indicated with green/gray text. Image credit: Digamma.

as CBD. In setting up such a cultivation facility, prospective hemp farmers were concerned about the psychoactive substances that traditionally triggered federal Schedule I enforcement of cannabis cultivation. This motivated prospective farmers to seek strains or cultivars that were suppressed or entirely absent for the genes expressing the psychoactive compounds. These were generally believed to be THC and CBN, and due to the ease of decarboxylation allowing ***in situ*** generation of these compounds, their corresponding acid precursors THCA and CBNA (where available, if at all). The target compounds, at the time, were CBD and its precursor CBDA. We have illustrated a cannabinoid schematic from 2014 in Imageδ to help give an approximate sense of the chemical perspective the industry was perceiving at that time.

Although Imageδ has many similarities to Imageα which was made in 2022, a noticeable difference is the absence of semi-synthetic cannabinoids and fully synthetic cannabinoids. While fully synthetic cannabinoids are not connected to the pathways of the natural cannabinoids; the semi-synthetics are. The biggest changes from the landscape presented in Imageα from those in Imageδ is the addition of two reactions: first, the CBD → Δ8THC reaction and, secondly, the HHC synthesis reactions. Both of the above reactions relate to the series of THC isomers known as the delta series (Δ).

The delta series was discovered when chemists observed that the double bond in THC can be re-arranged to several other positions. The natural THC isomer, the one produced by the plant, is Δ9-THC. As this double bond moves to other positions in its ring, it changes the delta number of the isomer. Originally it was believed that only Δ9-THC was psychoactive, but further investigation has shown that the other isomers in the delta series also show psycho-activity, although often with lower potency than Δ9-THC. As these THC isomers in the delta series are exposed to oxygen, the oxidation of each of them yields the same final



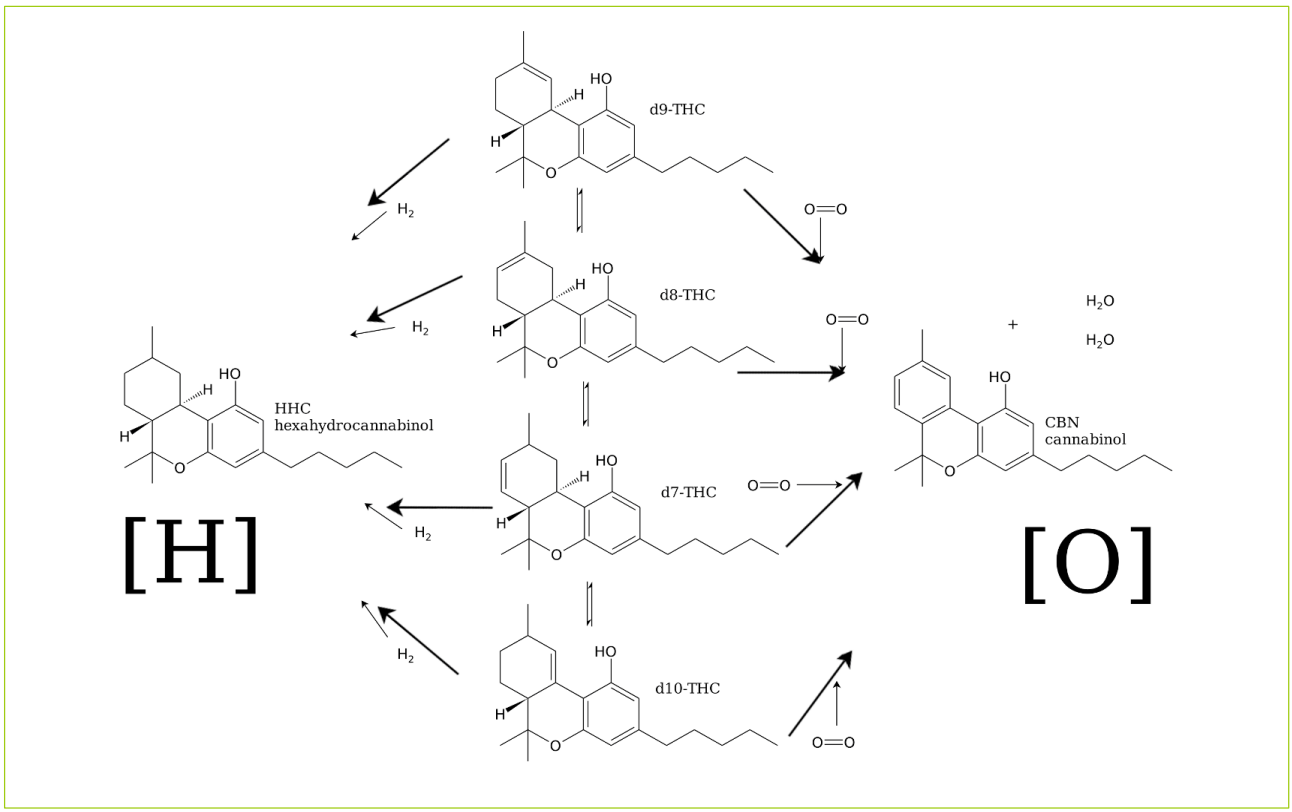
Imageδ – A skeletal diagram of the organic structures of the natural cannabinoids and their breakdown products from 2014, before California, Nevada, Maine, and Massachusetts recreational cannabis programs were passed by state legislators, and well before the U.S. federal government passed the 2018 Farm Bill. At that time, the CBD → Δ8THC reaction was not well known, and so the liability for psycho-activity for CBD producers was outlined as above, keeping THC-species separate from CBD or other non-psychoactive cannabinoid production. Note that chemical reactions, indicated by arrows, bear reaction names in this diagram. Image credit: Digamma.

product, CBN, regardless of which isomer from the delta series was the starting point. This is illustrated in Image**ε** for visual clarification with all reactants and products indicated, such as H_2, O_2, and H_2O.

What has changed significantly from 2014 to 2022 is the presence of a well-established class of reactions that can convert CBD to Δ8-THC. This is achieved through a variety of means but the most successful and popular reactions seem to use a Lewis acid as a catalyst. A Lewis acid is a type of acid that can temporarily store electrons, and this ability helps it to affect structural re-arrangements in a molecule. In particular, the Lewis acid helps to store electrons during the ring closing reaction that occurs between CBD and any THC isomer.

But this reaction rarely, if ever, produces Δ9-THC like the cannabis plant does naturally. This is because the Lewis acid's ability to affect structural rearrangement applies equally to both the ring closing reaction and the double bond rearrangement reaction. Due to this dual effect, the product of CBD ring closure is most commonly the Δ8-THC isomer. We have illustrated this reaction in Image**ζ** to help demonstrate the relevant components. What this reaction does in tandem is close the third ring on the THC isomer while also moving the double bond from the Δ9 to the Δ8 position. Why does the Δ8 position emerge as the exclusive (or most common) product of the reaction? The answer has to do with thermodynamic properties of molecules called conformation energies.

The reason that Δ8 is the major product of the CBD ring closing reaction has to do with the stability of the double bond in various positions. Each position that the double bond could potentially be in the ring has a different effect on the thermodynamic strain caused by the deformation of a geometrically idealized ring. The natural product, Δ9, causes a strain on the left side of the ring, and the corresponding double bond on the mirror image side, Δ7, shows a reflexive strain on the opposite side of the ring. This strain is often described by chemists as "puckering" to signify the deviation from the planar flat ring that would



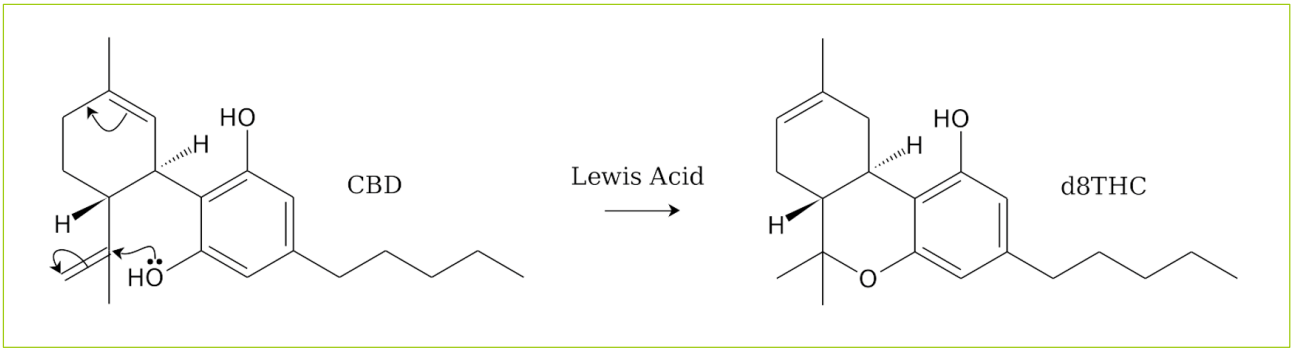
Imageε – A diagram illustrating the positions of the delta series of THC cannabinoid isomers in relation to two of their end-products: CBN, HHC. The first reaction shows the four isomers converting to CBN, the ***oxidation*** of 4H from each isomer in the delta series (right-facing). The second reaction shows the four isomers converting to HHC, the ***reduction*** of 2H into each isomer in the delta series (left-facing). Image credit: Digamma.

be the lowest energy state of the system. A chart showing the calculated thermodynamic energies of conformation for each THC isomer in the delta series combined with a three-dimensional illustration of the ring geometries with ring strain indicated is provided in Imageη.

Other than the conversion of CBD into THC delta series isomers, the other big innovation from the 2014 →2022 time period is the innovation of HHC, also known as **H**exa**H**ydro**C**annabinol.

The first reference to this compound was at the CannMed 2017 conference at Harvard Medical School Campus, where Mark Scialdone presented his creation of HHC, the process he used to make it from Δ9-THC, and how similar that process was to the process used by the food industry to convert plant oils into margarine. Scialdone confessed to smoking HHC experimentally to see what the subjective psychoactive effects where and to compare to Δ9-THC. When asked by one of the doctors in the audience what HHC felt like, he replied that it was similar to Δ9-THC but it made "his beard feel itchy" to a very distinctive cry of synchronized gasps from the largely clinically-trained audience in the lecture hall. Additionally, according to the discovering chemist, HHC was indeed a psychoactive substance.

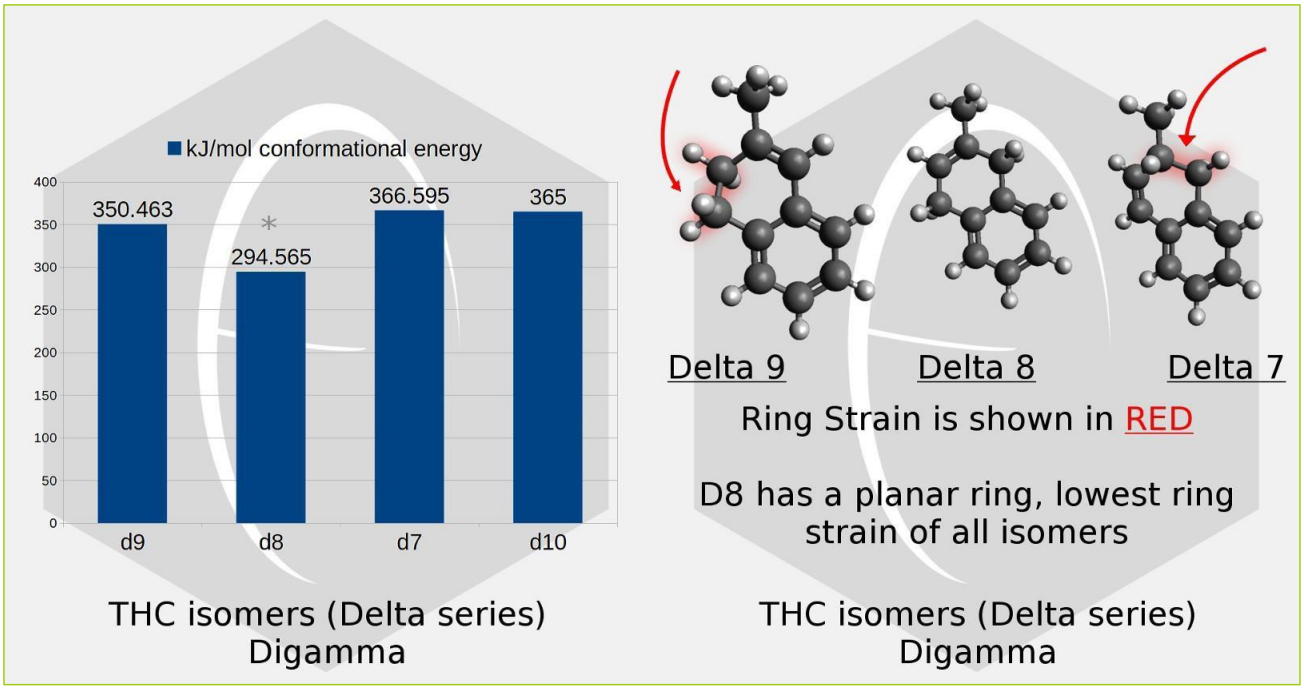
The chemistry of HHC is relatively simple to relate, especially when one has a good understanding of the relationship between CBN and THC, or **T**etra**H**ydro**C**annabinol. This name seems a bit odd, as the tetrahydro prefix makes it seem like a modification of an existing structure. The fact is that this is true because cannabinol (CBN) was discovered before THC, and so the root name of the structure goes to CBN as cannabinol. Because cannabinol has four hydrogens removed relative to THC, the proper name for THC was simply a cannabinol root with a tetrahydro- prefix attached. The fact that CBN is made through degradation of THC was not something initial



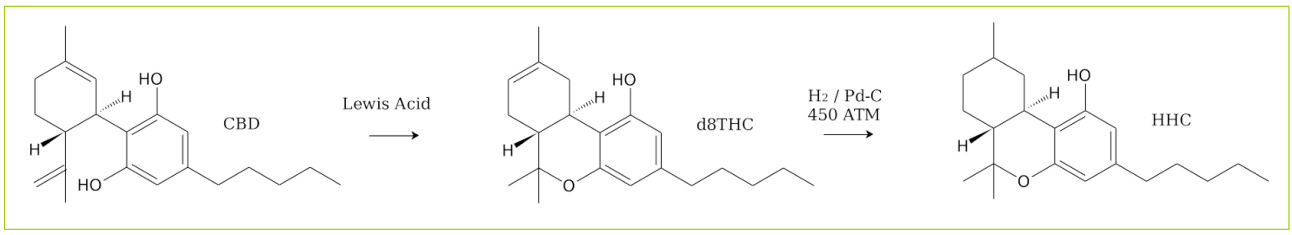
Imageζ – A diagram of the ring closing reaction that allows CBD to convert to Δ8-THC. This reaction is known to require a Lewis acid for effective yields. The Lewis acid, an electron acceptor, helps to close the ring in the reaction between CBD →THC, but also helps to cause the double bond re-arrangement into the Δ8 position. Image credit: Digamma.

scientists were aware of, as CBN is more stable than THC and early experiments most likely used old, processed (like hash), or cured cannabis products, which would have had a lot of THC that could have been oxidized to CBN. This is why the early experimenters identified CBN as the most abundant and stable compound and assumed it was the primary active ingredient in cannabis.

When Raphael Mecholaum published the first correct structures of THC and CBD in 1964 and 1965, respectively, both were shown to have a single double bond in the second ring in the Δ9 position. This explained why the natural cannabinoids have isomers in the delta series, which applies in parallel to both the THC and CBD isomer series. What this means is that all the delta isomers that



Imageη – Left: A diagram showing the calculated conformational energies of each THC isomer in the delta series. Right: A 3D illustration of the relevant geometries in each double bond position for each of the delta series, with ring strain indicated in red with a red arrow. Image credit: Digamma.



Imageι – A diagram of the ring closing reaction that allows CBD to convert to HHC through Δ8-THC. The second reaction requires gaseous hydrogen (H_2) with a platinum or palladium catalyst (platinum or palladium respectively). The first half of this reaction is shown in Imageζ. Image credit: Digamma.

exist for THC also exist for CBD and are known stable chemical structures, but CBG does not have delta isomers.

Adding two double bonds produces CBN, regardless of which isomer in the delta series was the starting point for the reaction. But what happens when the ring is stabilized not by completing the aromatic double bonds, but removing them altogether? This is the chemical structure of HHC, and like the production of CBN, it can use any THC isomer in the delta series as a starting point for its reaction. This concept was illustrated in Imageε previously for the reaction from THC delta series isomers to CBN and HHC. We have illustrated the reaction showing the anti-parallel reactions of oxidation (to CBN, right-facing) and reduction (to HHC, left-facing). Thermodynamically, CBN and HHC represent a downward and upward energetic step from the THC isomers in the delta series, both of which are stable endpoints for all the isomers in the delta series.

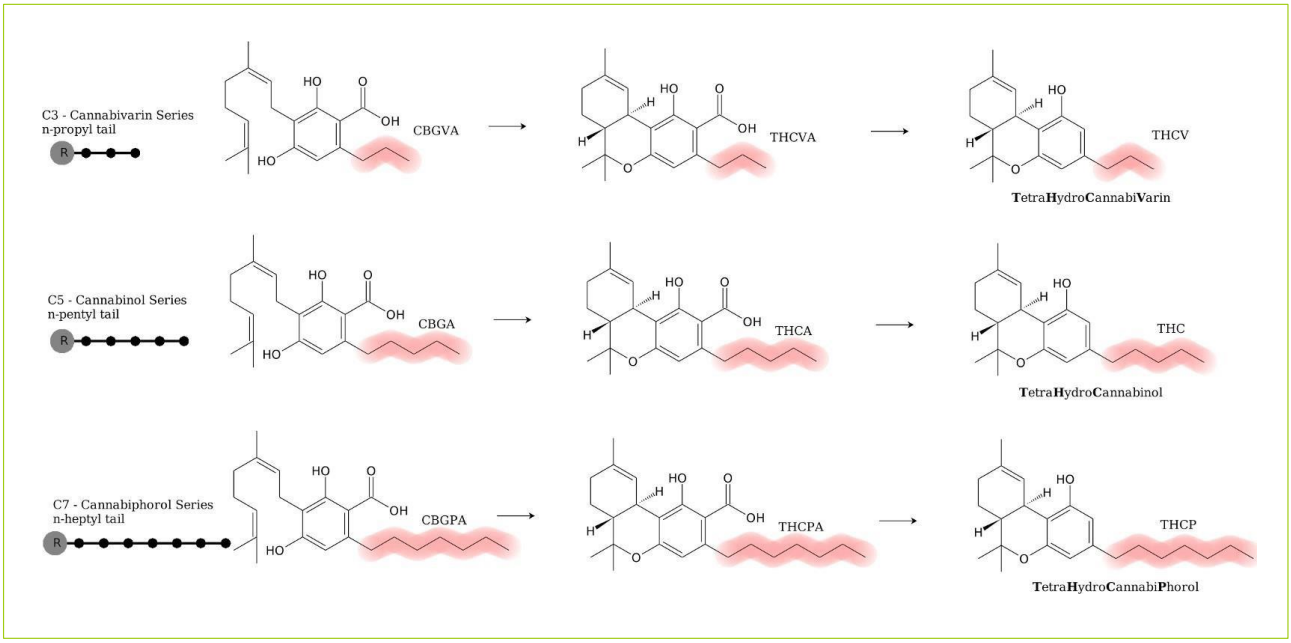
Returning our attention to the reaction outlined in Imageζ which shows how a Lewis acid can be used to catalyze a CBD ring closing reaction that produces Δ8-THC. When we combine the information in Imageζ with the information in Imageε, which showed how delta series can become HHC, we get a reaction starting with CBD and ending with HHC. We have reproduced this reaction mechanism in Imageι. The reaction, outlined in Imageι, uses the same technique used by the food industry to make non-spoiling margarine from plant oils. This conversion is done by catalytic hydrogenation with a platinum or palladium catalyst at several hundred atmospheres of pressure. This same process is used to convert a THC delta isomer to HHC.

What this reaction allows is for a producer with non-psychoactive compounds to convert to natural cannabinoids and semi-synthetic cannabinoids that are indeed psychoactive. The reactions outlined in Imageι allow a psychoactive cultivation system to exist that entirely bypasses Δ9-THC as a compound present on-site at a facility at any detectable concentration. The significance of the reactions from Imageι will be elaborated upon in the following section titled "Law" and more of the legal and business consequences of these implications will be discussed there. It is important to understand the chemical landscape from 2014, outlined in Imageδ, before studying the reaction mechanisms outlined in Imageι

What Imageδ does not have that Imageι introduces (and can be seen in Imageα) is a path from CBD to the THC delta series and therefore from non-psychoactive to psychoactive substances.

The final component of cannabinoid chemistry that must be covered is the pentyl tail analogue cannabinoids. Most traditional cannabinoids, such as THC, CBD, and CBG, have a five-carbon tail attached to them called a pentyl tail. When this tail is swapped out with a three-carbon tail, called a propyl tail, THC becomes THCV, CBD becomes CBDV, and CBG becomes CBGV. What THCV stands for is **T**etra**H**ydro**C**annabi**V**arin. The -varin ending indicates that the traditional pentyl tail has been replaced with a propyl tail.

When the pentyl tail is not replaced with the propyl tail but rather a seven-carbon tail called



Imageι – A diagram of the ring closing reaction that allows CBD to convert to HHC through Δ8-THC. The second reaction requires gaseous hydrogen (H_2) with a platinum or palladium catalyst (platinum or palladium respectively). The first half of this reaction is shown in Imageζ. Image credit: Digamma.

a heptyl tail, then the suffix switches from -varin to -phorol. THC becomes THCP, which stands for **T**etra**H**ydro**C**annabi**P**horol, with analogous names for CBDP and CBGP as well.

Although THCV is more well known in the cannabis community than THCP, which seems to be a more recent phenomenon, there are other pentyl tail analogues of cannabinoids that are known. THCO is the acronym given to the one-carbon tail analogue (this is called a methyl tail) and stands for **T**etra**H**ydro**C**annabi**O**rcol. Although many of these pentyl tail analogues are considered to be semi-synthetic, they have been known to occur naturally in cannabis plants for many years through THCV and the strain Doug's Varin. These isomers seem to be formed upstream from the formation of CBG and seem to be made upstream from the synthesis of olivetolic acid (OA) when the pentyl tail is added to the OA molecule. Although the genes that govern this are still not well understood, THCP, THCV, THCO and other pentyl-tail analogues that are reported to have various levels of psycho-activity are known to exist in the cannabinoid supply chain and do not formally meet the chemical definition of Δ9-THC. Evidence of THCV acting as an antagonist to Δ9-THC ability to stimulate appetite are known, making it an appetite suppressant. Data on THCP seems to indicate the elongation of the pentyl tail has the reverse effect as shortening, with a stronger cannabinoid binding strength of THCP to the CB_1 receptor relative to Δ9-THC.

We have illustrated the biosynthetic pathways for THCV, THC, and THCP respectively from top to bottom in Imageκ. The carbon tail is illustrated by diagram on the far right, and the CBG →THCA → THC pathway is illustrated for each.

Now that we have covered the relevant chemistry that governs these cannabinoids, we can progress to the legal implications of these compounds and how they are regulated and legally distributed at this time.

LAW

The laws surrounding cannabis are complex and spread over a rather long history, so the information has been organized chronologically to help create a linear narrative on the evolution of cannabis laws in the U.S. Both federal and state laws will be included with the most relevant state laws on the evolution of the cannabis legalization phenomenon being given an emphasis.

Marihuana Tax Act of 1937

The marihuana Tax Act was one of the first federal laws to regulate cannabis in the U.S. This act taxed cannabis and was drafted by Harry Anslinger, the commissioner of Federal Bureau of Narcotics. This act stayed in effect until it was repealed in 1969 and replaced by the Controlled Substances Act the following year. Although this act established the federal prohibition of cannabis with the main justification being the psycho-activity of the cannabinoids it produces.

Although this law can be seen as one of the foundational elements of the prohibitionist laws and enforcement throughout the second half of the 20th century often called "the war on drugs", it is believed that the motivation behind the bill was to stop the growth of the industrial hemp industry. William Randolph Hearst, a newspaper magnate who was riding the "yellow journalism" wave to great success, was heavily invested in timber to supply the pulp for his newspapers and feared that the growth of the hemp industry would threaten both his timber investments and his media empire. Andrew Mellon, then secretary of the Treasury, had invested heavily in Du Pont's newly patented chemistry process for making stronger, synthetic fibers from petrochemicals called "nylon". Both individuals had strong financial reasons for the hemp fiber industry to either fail or stagnate.

Regardless of the reason, the importance of the 1937 act is that it established for a generation that the federal government had the right to tax and prohibit certain substances. Young people growing up in the period between 1940-1970 were internalizing a system of drug prohibition. By the year 1970, a pattern of prohibition was accepted as established practice by late 20th century Americans.

Controlled Substance Act of 1970

The Controlled Substance Act (CSA) of 1970 is a foundational document in the establishment of widespread drug prohibition in the late 20th century American history. The bill itself was signed by President Richard Nixon and created several familiar elements of drug prohibition, including the drug category system known as "scheduling" of controlled substances, as well as a federal agency called the Drug Enforcement Agency (DEA).

Before 1970, federal drug issues were handled by two agencies, the Bureau of Narcotics and Dangerous Drugs (BNDD) and the Office of Drug Abuse Law Enforcement (ODALE). The FDA received recommendations from both agencies on May 1, 1970, for scheduling of controlled substances in the CSA Bill. Shortly after, on June 1, 1970, Nixon combined the two agencies to form the DEA.

Part of these joint recommendations from the DEA-FDA input was to assign schedule numbers to each controlled substance. There are three components considered when assigning a schedule for a drug, the first being its potential for abuse, the second is the presence of accepted medical uses, and the third consideration is the factors of safety and addiction. Depending on the risk factors in these three categories, the drugs are assigned a schedule number, starting with I as the most prohibitive with no accepted medical use, and schedule V as lowest potential for abuse.

Much like the marihuana Tax Act of 1937, the CSA was a federal strategy to bring national unity to a problem that had significant diversity in law and enforcement on the local level. While many states in the early 20th century passed laws regulating and taxing both the hemp and marihuana forms of cannabis, it was not until 1937 that a federal law unifying the national landscape came about. The CSA in 1970 functioned much in the same way, creating sweeping federal precedent for the patchwork of local drug enforcement laws at the state level. As the CSA was being passed

through Congress, the Justice Department under John Mitchell was authoring and sharing drafts with justice departments of state-level versions of the CSA with very similar language and legal structure as the federal bill. This not only established a unified federal code for prohibition and enforcement of drug laws, but also established agreement between federal and state policy surrounding controlled substances in the U.S. This intention, to have federal and state law in complete alignment, is the exact opposite of what has happened in the modern legal scenario with the Cole Memorandum of 2013, discussed below, where state and federal laws are in direct contradiction.

The important legal consequence to focus on is the schedule system that was created in 1970. Schedule I substances, such as heroin and LSD, have no accepted medical use and are known to have high potential for abuse and addiction. In the original text of the CSA, Schedule I substances are listed under section 202 sub-section (c) where hallucinogenic substances are covered, and "Marihuana" is listed as item 10. One method of relating the three terms for cannabis is that the first is the species genus name, and marihuana and hemp are terms used to describe that species cultivated for drug and fiber cultivation respectively.

The consequences for listing a plant species among a category designed and inhabited by molecular species are significant and not readily evident. Other residents of the Schedule I category are popularly known substances, mostly as illicit drugs, but are always listed as a chemical compound and not as a biological species. LSD was listed above and is a part of the tryptamine class of compounds. Tryptamines are compounds that mimic the serotonin structure and target its 2A receptor sub-type, among others, and typically induce a psychedelic experience in users. Other tryptamines on Schedule I include psilocybin and psilocin, the active ingredients in Psilocybe species and other closely related mushroom species, sometimes called magic mushrooms.

Psilocybe mushrooms are an excellent comparative example to cannabis in the legal language of the CSA. The other Schedule I substances listed in the above paragraph were each molecular species, a specific chemical compound. With Psilocybe mushrooms, we see the active ingredients listed as chemical compounds regardless of the biological source and the biological species associated with them. If Psilocybe mushrooms were listed in the same manner as cannabis, the text would read something like "magic mushrooms". A more scientific name would be "***Psilocybe cubensis***" or "***Psilocybe mexicana***". Instead, the CSA continues with a pattern of criminalizing chemical compounds and not biological organisms, except in the case of cannabis or "Marihuana".

If the CSA had consistent language for cannabis as it did for other Schedule I residents, then the compounds Δ9-THC, CBN, and any other cannabinoid that is considered an active ingredient to the recreational consumption of cannabis would be listed. Such legal language would have automatically excluded all non-psychoactive compounds discovered in that same organism, whether discovered before or after the bill's signing. In the example of cannabis, this would apply to CBD and the other non-psychoactive cannabinoids. But the inclusion of the term "Marihuana" makes this interpretation difficult.

Additionally, references to THC are made in the CSA on line 17 with "Tetrahydrocannabinols." The term tetrahydrocannabinols is somewhat ambiguous, as it seems to reference the THC delta series due to the use of plural. This language also seems to exclude psychoactive substances such as CBN and HHC, which are not "tetrahydrocannabinols", as well as the non-psychoactive substances such as CBD and CBG. The original language has been amended to "Tetrahydrocannabinols, except for tetrahydrocannabinols in hemp (as defined under section 1639o of title 7)". This change is a reference to the 2018 federal farm fill, which is covered later in this section.

Even infamous drugs that have caused social harm around the world, such as cocaine and methamphetamine are placed on the Schedule II category in the CSA. This is because there are medical uses that can establish the accepted medical component of the scheduling decision, even if the abuse and addiction elements are very

unmanageable. A medical application for eye surgery protects the Schedule II status of cocaine. When compared to other topical anesthetics in the same chemical class, such as lidocaine and Novocain, cocaine molecules have a better outcome with the nerves of the eye, and so an application is medically justifiable for ophthalmic surgery. Much like cocaine, methamphetamine is included in Schedule II rather than Schedule I because of its links to an FDA-approved drug called Desoxyn (generic is called methedrine), which is prescribed to children as young as six years old for symptoms relating to Attention-deficit/ hyperactivity disorder (ADHD). Juvenile pharmacology will make another appearance in the following two sections, covering California's first medical cannabis program in the U.S. and Colorado's first recreational cannabis bill, as the need to give juveniles with seizures caused by Dravet syndrome a safe and reliable source of CBD.

Proposition 215 (CA 1996)

Proposition 215 in California was the first medical cannabis initiative authored by a state government in contrast to federal prohibition. The bill had many authors, including Dennis Peron who was an activist advocating for the use of cannabis to treat the HIV/AIDS crisis that was impacting the San Francisco Bay Area. After passing with 55% of the popular vote in 1996, clarifications and administrative considerations were expanded in Senate Bill 420 in 2003.

The new Californian system was simple enough: if anyone had an "herbal recommendation" from a doctor, they were allowed entry into medical dispensaries to purchase cannabis. The doctor needed to be properly licensed and willing to give an "herbal recommendation" for cannabis for the patient's health, a document that was valid for one year and cost usually under $100. Finding doctors who were willing to formally recommend cannabis was difficult at first, but then a system emerged where doctors who advocated for cannabis would advertise herbal recommendations for practically anyone who made an appointment. Symptoms as general as anxiety and insomnia were acceptable, creating an accessible system.

The term "herbal recommendation" is a contrast to a prescription, which is connected to controlled substances and their classification under the federal system. Instead, the doctor is merely recommending a natural herbal remedy based on symptoms, and that document justifies entry, purchase, and possession of cannabis according to the laws of California, in a sort of federal by-pass. Other peculiarities of the California medical system included a cooperative system where cultivation facilities were actually collectives. Members' rights to grow plants were essentially transferred over to the collective who organized a large grow and distributed the harvest to the members. What this often became was a dispensary where first-time members would have to register as part of the collective before walking in and shopping, which followed the practical retail model but was legally still a collective of medical patients who simply did not have the time or resources to cultivate their own medical plants.

Apart from issues in the business structure of the growing medical cannabis industry in California, the legal aspects were being contested between federal and state authorities. This led to many state-legal cannabis operations being raided by federal DEA agents and the operators arrested under CSA violations. The case of Oakland Cannabis Buyer's Cooperative even made it before the Supreme Court in 2001, which ruled in favor of federal authority to schedule substances and enforce federal law.

With this precedent in place, an era of federal raids on California cannabis operations began. The federal prosecutor Melinda Hague was routinely pursuing the big-name Bay Area cannabis dispensaries, such as CBCB (Cannabis Buyers Club Berkeley) and Harborside in Oakland, to name a few. The Cole Memorandum of 2013, covered in a section below, brought an end to federal enforcement on state legal operators in practice for a time.

The success of cannabis in treating HIV/AIDS patients in San Francisco in the late '80s brought about a pharmaceutical product, Marinol, which is a synthetic Δ9-THC preparation in sesame oil, for treatment of HIV/AIDS wasting syndrome and a few closely related syndromes. In 1986, the DEA rescheduled Marinol from Schedule I to Schedule II. It was found that many of the other broader benefits of whole plant cannabis were not seen

in Marinol, which showed clinical effectiveness only with the wasting syndrome and stimulating the appetite. This evidence pointed to a possible entourage effect in whole plant cannabis that may not be transferable to the isolated components.

Amendment 64 (CO 2012)

With the advent of recreational cannabis bills passed in 2012 in Colorado and Washington, the cannabis industry changed again as the medical necessity of consumers was no longer necessary for purchase of cannabis. Dispensaries were now simply carding consumers at the door like bars to verify they were over 21, which opened the door to much wider markets for these dispensaries. Colorado being surrounded by states with more prohibitive laws, was seeing cannabis tourists boosting its industry revenue and state tax revenue was sharply rising. It is possibly at this time that the "green wave" concept of a rising and profitable industry started to become cemented in the public perception.

But as the industry expanded and cultivation and dispensaries became a common sight in Colorado, the proliferation of breeding stock and cultivation experiments led to many sought after CBD rich strains becoming known. This coincided with a growing recognition within the cannabis industry of a form of juvenile epilepsy called severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome. This disorder causes severe seizures starting in infancy which often progress and become worse, causing a large number of seizures often numbering in many per day. The seizures are so common and disruptive that normal growth and development of the child is impaired and often results in life-long severe disability.

What was discovered was that high doses of CBD stopped many Dravet-related seizures, in some cases with such effectiveness that seizures would almost cease and the child could resume normal development. But because isolated CBD was not widely available at that time outside of Colorado, many families with children with Dravet syndrome had to relocate to Colorado to treat their children. A famous example is Charlotte Figi, the patient who gave her name to the strain Charlotte's Web, which was a high CBD, low THC cultivar intended to treat children with Dravet syndrome.

Given the miraculous nature of CBD to reverse the course of a disastrous disorder, it seemed that the acceptance of CBD in mainstream medicine was the natural next step. And GW Pharmaceuticals received approval for Epidiolex, a CBD oral preparation for Dravet syndrome, and rescheduled Epidiolex (but not CBD) as a Schedule V substance. This allowed physicians to prescribe the product to patients within federal law but left the legal status of CBD even more nebulous at the federal level.

Additionally, studies have shown that CBD alone is not sufficient to stop all forms of seizures in Dravet syndrome patients. Some studies from Israel have shown some other rare cannabinoids that are co-present with the CBD extract that are necessary for the final effect, which are often absent from the pharmaceutical preparation of Epidiolex. The studies discovered these rare and trace level cannabinoids when following the outcomes of a juvenile patient who was receiving CBD extract from a local grower, whose crops had slight genetic drift from harvest to harvest. The scientists were able to identify that this drift lost these trace components and was correlated with the return of the seizures in the patient. This is similar to the lack of efficacy the pharmaceutical industry experienced when patenting THC as Marinol for HIV/AIDS wasting syndrome, and both examples indicate the entourage effect as the most likely explanation for the effects lost from whole-plant cannabis and its extracts.

Cole Memorandum of 2013

The Cole Memorandum effectively ended the federal enforcement of federal cannabis law against state legal programs. The new Justice Department policy stated that distribution of non-medical cannabis would be tolerated in states where it was legalized, except were firearms or interstate commerce were involved. This put an end to the raids and legal battles that state legal operators had to contend with and was a big step towards the legitimization of cannabis business.

The effect was reinforced through the Rorhabacher-Farr amendment the following year. The amendment prohibits the Justice Department from spending funds on the enforcement of federal cannabis law on state medical cannabis programs. The amendment expires annually and must be renewed every year, and last expired September 20, 2022.

Attorney General Jeff Sessions rescinded the Cole Memo in 2018 but few prosecutions have been seen from the DEA since. The Rohrabacher-Farr amendment, if it continues to be renewed, will prevent an Attorney General hostile to state legal cannabis from taking significant action, as it most likely had done in the case of Sessions' tenure and its lack of federal raids.

Recreational Bills of 2016 (CA, NV, MA, ME)

This section covers a tipping point in the political climate of the U.S. cannabis industry. In November 2016, four states, including the largest by population and GDP, legalized recreational cannabis at the state level in the footsteps of Colorado and Washington. Mainstream acceptance of recreational cannabis was at a tipping point, where a phenomenon seen while stopping over in Denver was now seen on both U.S. coastal population centers.

After this moment, a return to federal enforcement seen under the Bush administration during the early days of California's medical system was no longer politically tenable. Attorney General Jeff Sessions, incoming with the Trump administration after November 2016, was infamously hostile to cannabis and was quoted saying, "Good people don't smoke marihuana". In alignment with that philosophy, he promptly rescinded the Cole memo in 2018. But aside from the above-mentioned Rohrabacher-Farr amendment from Congress blocking Sessions from using a single dollar for a raid on a state legal cannabis operation, the political climate in the U.S. had shifted. Although finally in the political position to stop the legalization phenomenon, Sessions, as the Attorney General, no longer possessed the political capital to carry out such actions.

Farm Bill of 2018

Leading up to 2018, the legal situation for various cannabinoids was becoming both fluid and confusing. CBD had been rescheduled to Schedule V but only as the Epidiolex formulation, and yet CBD products were sold online and in smoke shops in all 50 states. The terms in the CSA, "Marihuana" and "Tetrahydrocannabinols" seemed to not cover CBD as a controlled substance, but the FDA had not approved it as an ingredient in food or supplements. A lot of the CBD seemed to be sourced from hemp farms that were allowed under clauses in 2014 Farm Bill, such as allowances for Indian Tribes and universities performing research. But as the amount of CBD being produced through hemp increased dramatically in the years since 2014 and 2018, a comprehensive solution was necessary.

This is where the 2018 Farm Bill changed things by defining hemp. The definition of hemp in the Farm Bill is included in the opening line of Title X Horticulture, Sub-section G Hemp: "The term 'hemp' means the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."

When compared to the more nebulous terms in the CSA, the Farm Bill seemed to be very clear-cut. It defined a specific molecule, Δ9-THC, as the active ingredient that would make a cannabis plant a controlled substance, the CSA's "Marihuana". The amended language in the CSA also notes that "Tetrahydrocannabinols except those derived from hemp" seems to exclude any cannabinoid that was sourced from hemp from the CSA.

"*Cannabis sativa* L." as it appears in the Farm Bill is categorized as a legitimate biological species. The language describes the Latin binomial name derived from Linnaeus' biological classification system from the 18th century. In fact, the capital

L. after many biological species names is a reference to Linnaeus' name and indicates that they are one of the species named in his 1735 publication of *Systema Naturae*, a scientific text that proposed a taxonomic system for classifying plants, one that is still used today. But unlike the CSA, the Farm Bill identifies biological species with a precision that the more cultural term "Marihuana" does not. Additionally, it defines hemp as a biological species with a condition of a certain chemical concentration, which is a much more precise legal and scientific definition. As covered in the section on the CSA above, the terms hemp and marihuana are used to express human intent when cultivating the same species of plant, *Cannabis sativa* L., making them imperfect definitions for legal status as they are tied to the cultivators' intent and, by implication, the breeding history of the cultivars, rather than a chemical concentration that can be measured and used as evidence in court.

Additional clauses in the Farm Bill shed light on some of the legal regulations that apply to hemp products that cannot apply to state licensed cannabis products. The authority to change other laws, such as the CSA, which has added a reference to the first section of the Hemp Sub-section G defining hemp, is included in 7 U.S. 1639r. The right of inter-state transportation for hemp products is defined in Section 10114, which explicitly states that nothing in the Farm Bill prohibits inter-state commerce of hemp or hemp-derived products [7 U.S. 1639t]. These changes are in direct contrast to the lack of progress many politicians and activists have had to implement for natural cannabinoids like Δ9-THC. These clauses support the direct contrast that is being seen in federal hemp versus state cannabis enforcement, with the right of inter-state commerce being a very significant advantage over state cannabis operators.

But with the laws being set up in this way, many producers could cultivate CBD producing plants and then convert them into psychoactive substances other than Δ9-THC, not triggering the enforcement of the CSA. A law that was passed for industrial hemp and non-psychoactive cannabinoids such as CBD was now giving semi-legal federal status to producers of psychoactive cannabinoids, such as Δ8-THC and HHC, as they were classified as hemp derived in the laws.

This created a wave of Δ8-THC gummie producers who sold their products in smoke shops and online across the 50 states. Many expected federal raids from the DEA or cease-and-desist letters from the Justice Department or the FDA. But instead a federal court ruled that Δ8-THC was legal if derived from hemp. In May 2022,making a ruling on *AK Futures LLC v. Boyd St. Distro, LLC*, the Ninth Circuit Court of Appeals decided that the Farm Bill defines hemp derived Δ8-THC as federally legal. This ruling took away the threat of federal enforcement against producers of hemp-derived psychoactive cannabinoids and allowed the growing federal recreational hemp market to keep expanding.

But the legal status of Δ8-THC with the FDA is still uncertain. It seems that like the FDA's perspective on CBD applied to Δ8-THC as well, that any marketing for medical conditions would be illegal until after GRAS applications and much evidence-based data. GRAS stands for **G**enerally **R**ecognized **A**s **S**afe, an important FDA status for a compound to be considered "safe". It seems that being defined as outside the CSA but not yet within the FDA GRAS list puts both CBD, Δ8-THC, and other cannabinoids in a gray zone between criminal enforcement and accepted medical use.

Where the FDA seems to feel very differently between Δ8-THC and CBD is in the psycho-activity. Whereas CBD's non-psychoactive properties make it less concerning when the market expands rapidly across the U.S. the proliferation of Δ8-THC has essentially brought recreational cannabis to all 50 states overnight. The FDA has reports of the dangers of Δ8-THC marketed as a "legal high" and is concerned about the harsh chemicals needed to transform CBD into Δ8-THC.

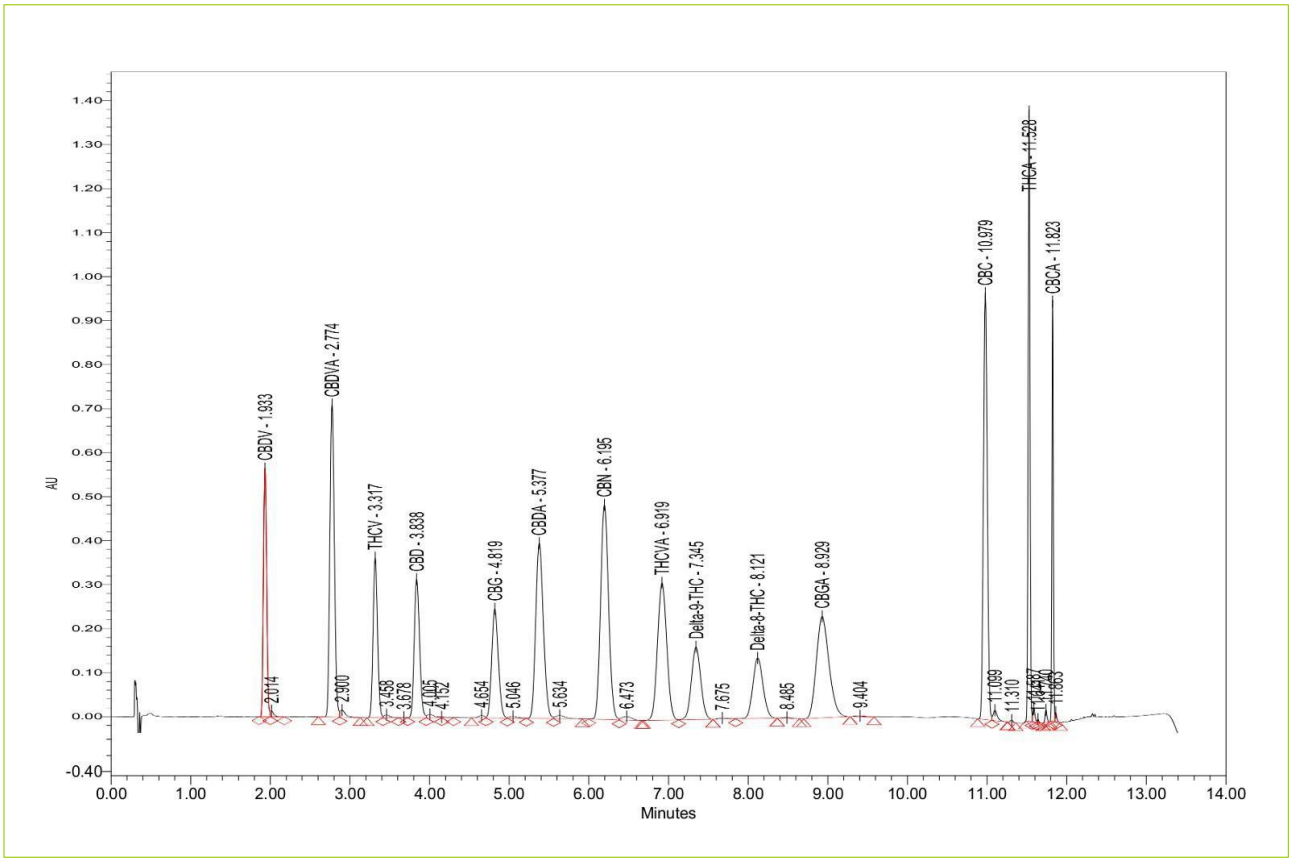
The FDA is correct about safety concerns, as the supply chain for recreational hemp Δ8-THC products looks very different from a state-licensed dispensary's process for making Δ9-THC products. In the following section, which focuses on chemical analysis for safety and labeling, these issues are covered. Labeling is a process with ramification for the legal status of products that must be defined as "hemp" or "marihuana" under federal law.

ANALYSIS

This section is about the analytical chemistry done on hemp and cannabis products. There are several elements that relate directly to business and law aspects of the cannabis industry that are covered in this section. We start with chromatography and how compounds are separated, with an emphasis on the distinction between Δ8- and Δ9-THC. The separations are followed by matrix interferences, which can interfere with accurate quantification of a compound, and the standard quality control used in the analytical chemistry industries to combat such sources of inaccuracy. The section closes on the testing requirements for state cannabis compared to federal hemp, with an emphasis on the differences in safety and contamination testing. A deep understanding of how analytical chemistry instrumentation works is not within the scope of this section but references to such works are included.

The best place to start is the chromatograph, the output of the analytical instruments that perform the analysis. Each separated compound is shown as a Gaussian peak separated along the horizontal x-axis. In Imageλ we have shown a 14-cannabinoid chromatograph showing the separation of pure calibration standards at the same concentration, with each peak labeled by individual compound.

Because the separation of compounds is critical to accurately measuring them, the separation of each peak from the next is an essential component of an accurate analysis. This is called baseline resolution, when peaks are completely



Imageλ – Above is a chromatogram of a 14-cannabinoid analytical assay performed on calibration standards of equal concentration for each cannabinoid. The chromatogram shows the instrument detector responding to each compound as it elutes from the separation column. The retention time of each compound, in minutes, is indicated on x-axis label. From a Waters Acquity with a TUV detector from a state cannabis lab in Missouri.
Image credit: Digamma.

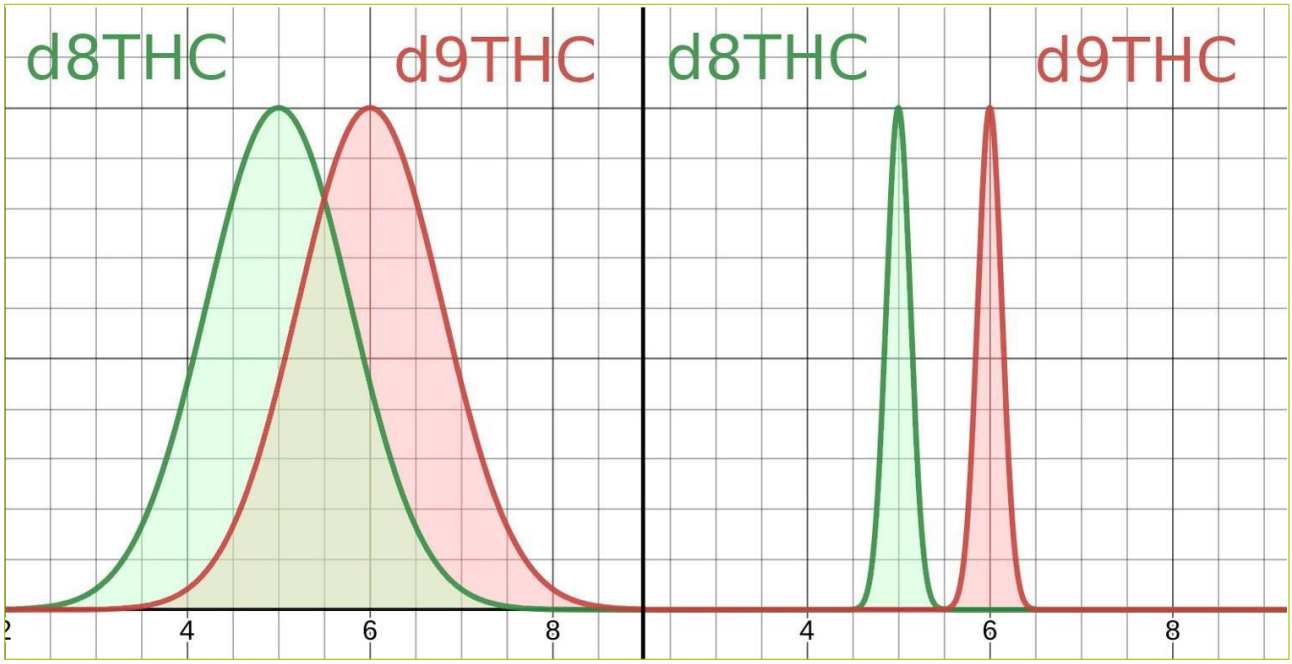


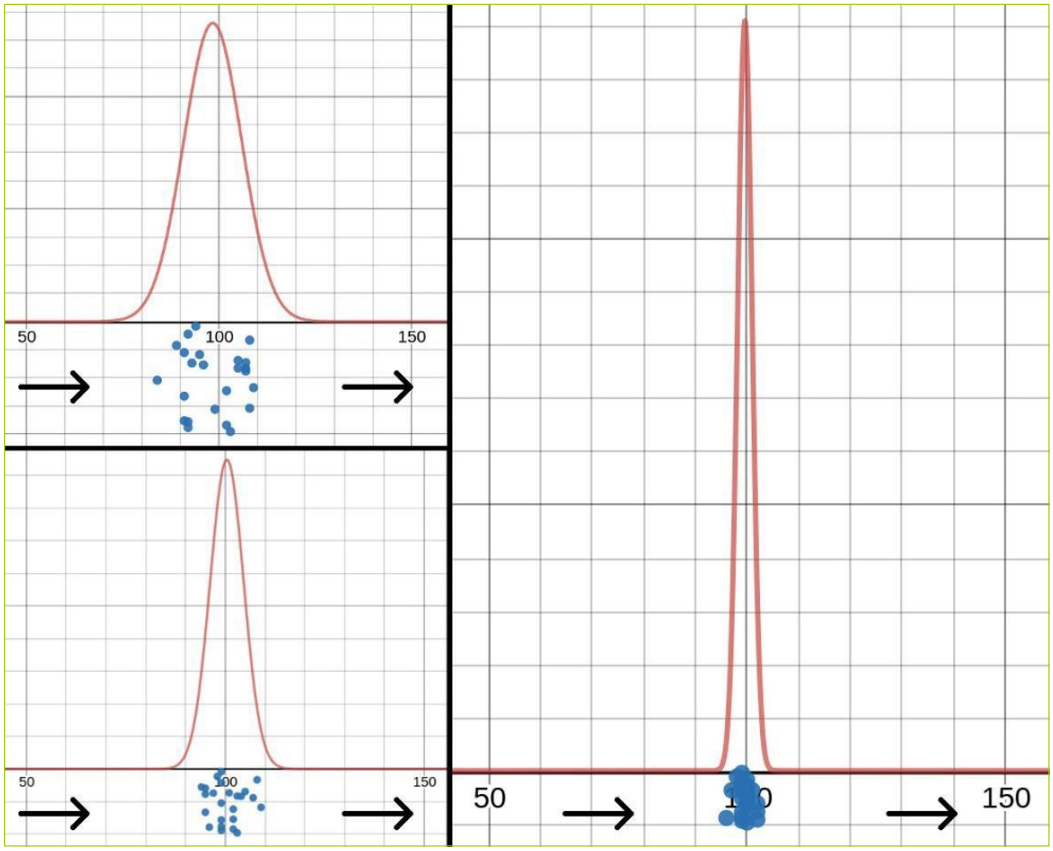
Image μ – An illustrative example of the effect of chromatographic resolution on separating structurally similar chemical isomers. The examples used here are the isomers of THC in the Δ8 and Δ9 form (labeled in **green** and **red** respectively). The image to the left shows a low-resolution separation where the two compounds co-elute (overlap) and cannot be independently measured with accuracy. The image to the right shows the same isomers with the same retention times, but with much higher chromatographic resolution, causing the peaks to elute separately (no overlap). Image credit: Digamma.

separated down to the chromatograph baseline. Achieving baseline resolution between very similar compounds, such as Δ8- and Δ9-THC, can be difficult and may require more advanced instrumentation. Chromatographic resolution is defined as the width of the Gaussian peak, and so an increase in resolution describes a decrease in peak width. In Imageλ the highest resolution is seen at the beginning and end of the chromatograph with a lower resolution peak in the middle of the graph around minutes 7-9.

Insufficient resolution can cause improper measurement of the target compound if they overlap with each other. The overlapping of chromatographic peaks is called co-elution and is a known issue in analytical chemistry. In Imageμ, an example of two co-eluting peaks, Δ8 and Δ9, are shown with low followed by high resolution. In the low-resolution image, the two compounds co-elute and the accurate measurement of either peak is no longer directly possible, as the overlap interferes with the total quantity. Additionally, teasing out two separate concentrations for two compounds is nearly impossible if the peaks are not fully separated. In the high-resolution rendition, the peaks are resolved to a much higher resolution and are much tighter, giving baseline resolution between them allowing for the accurate measurement of both compounds. To better understand how labs achieve high resolution and accurate measurement of cannabinoids, we look at the spatial distribution of target compounds in the instrument.

As the target compounds are separated from each other, they are distributed spatially in the chromatographic column in a diffuse cloud. When the cloud becomes more spread out, the peak becomes lower and wider, with lower resolution. As the cloud becomes densely compressed, the peak becomes taller and tighter, with higher resolution.

The tightness of the compound grouping can rely on many factors, as was illustrated in the

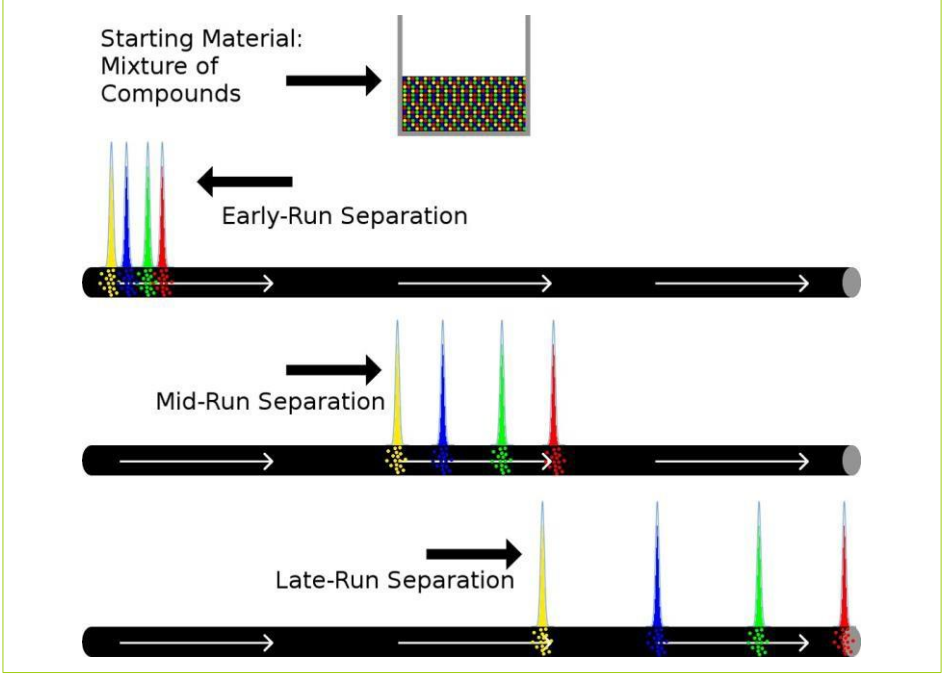


Imageν – An illustrative example of the relationship between chromatographic resolution and the compound distribution. The diagram relates a Gaussian function in **red**, showing the detector signal over time, and the distribution of compound particles in the column, shown in **blue**. The tighter the distribution of particles in the column, the higher the chromatographic resolution of the Gaussian curve read by the instrument's detector. Image credit: Digamma.

chromatograph in Imageλ to vary across the length of the chromatograph. This is because the rate of elution varies through the chromatographic run, changing the distribution of particles and thus the Gaussian peak shape. These subtle variations are dependent on the specific analytical method that a laboratory is running, but as long as all target compounds are baseline resolved the results are equivalent within an acceptable margin of error. To examine how we can increase chromatographic resolution across the entire chromatographic run, we will have to examine the chromatographic column and the variable of its length.

To understand the effect of column length on chromatographic resolution, it helps to start with this understanding: because the column separates compounds, the longer the column, the better the separation of compounds and therefore resolution. To help illustrate this effect, we have shown the separation of model compounds in a mixture in Imageξ. What this image helps to illustrate is that longer columns may be necessary to separate very close compounds, like the delta series of THC isomers.

Aside from co-elution of target compounds, another major interference on the accuracy of a reported lab result can be matrix interference. Matrix interference is a Gaussian chromatographic compound just like the target but is defined as a non-target compound present in the sample matrix (or substance or material). When these compounds co-elute with target compounds, the measured peak may be under-reported or missed altogether (false negative). The matrix interference can often be under much lower resolution with

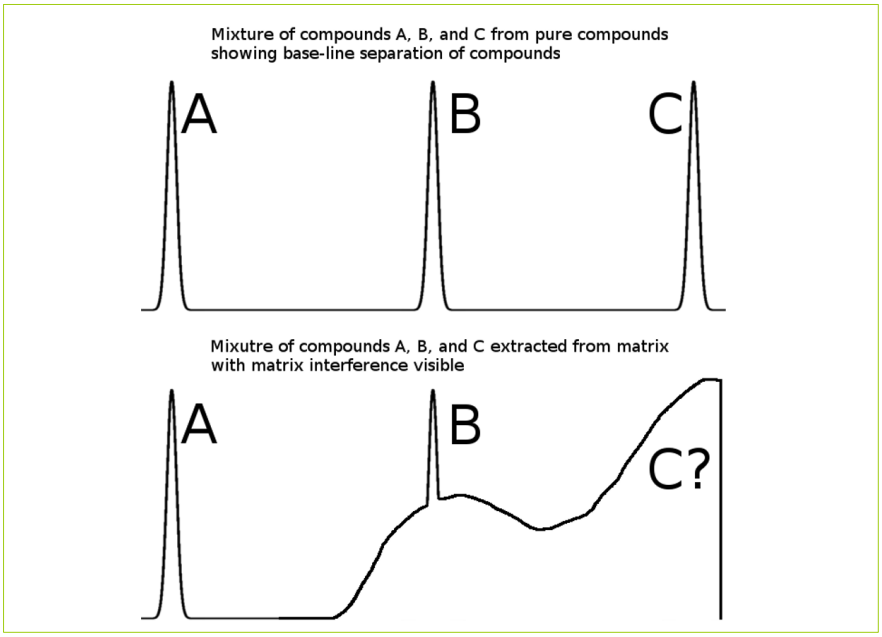


Imageξ – An illustrative diagram showing how chromatographic separation works in theory, as applicable to both gas (GC) and liquid (LC) chromatography. The mobile phase is contained within the column and shown in as black tubes, with the mobile phase passing through it as while arrows. The diagram shows how the column separates four compounds, **yellow**, **blue**, **green**, and **red**. The compounds travel through the column with variable resistance and become organized from an even mixture (pictured on top) to perfectly separated compounds eluting from the column (pictured on bottom). The diagram also illustrates how the chromatographic resolution increases with column length. Individual particles with an approximate spatial distribution are shown within the column with Gaussian peaks simulating the detector signal resting on the top of the column. Image credit: Digamma.

broad, sometimes meandering, curves. This widening of matrix effects is often because the analytical method was optimized for target compounds, which come out in high resolution, but other substances may not be under optimal conditions and may form these broad shapes.

The way analytical labs combat these effects on the accuracy of the data is by having quality control that shows a lack of interferences and that all target compounds are being detected with accuracy. There are many complex terms in the quality control world of analytical chemistry labs, such as quality management system (QMS), laboratory information software (LIMS), as well as validation and method development. The process certifying the accuracy of an analytical lab is quite a rigorous process, made more challenging by cannabis specific legal restrictions. State labs must seek a license from the state department regulating the cannabis program, and often seek an ISO 17025 accreditation as well. Cannabis labs have two choices in ISO 17025, Perry Johnson Laboratory Association (PJLA) and American Association for Laboratory accreditation (A2LA). Federal hemp labs are also required to have a DEA anti-diversion license after January 1, 2023, which mostly focuses on the ability to safely receive and store-controlled substances with a minimization of risk of diversion to the community.

What we have reproduced below with Image[1] is a sample of a certificate of analysis from a cannabis lab reporting on 11 cannabinoids. The rows colored in green are quality control (QC) samples that are run as part of the QMS. These include blanks to rule out false positives (PB and MB), positives or spikes to rule out false negatives and under reporting, and some calibration verification before and after the client samples to prove accuracy throughout the run (ICV and CCV) with a final blank at the end to rule out



Imageo – An illustrative example of how interferences can affect the quantitation of certain compounds in chromatography. In the top, compounds A, B, and C are shown eluting with more than baseline resolution. In the bottom we see the presence of an interfering signal from non-target compounds cover up part, as in compound B, or all, as in compound C, of a detected peak. Image credit: Digamma.

cross contamination. Many regulated analytical chemistry industries require a calibration check after every 10 client samples to re-verify calibration and demonstrate accuracy of all samples in the batch without exception. The FDA and EPA have similar requirements in place, as well as specific version of the matrix QC samples run at the beginning of the batch.

Now, many state cannabis programs have requirements modeled after the EPA and FDA guidelines. But, ultimately, federal chemistry guidelines cannot apply to an industry that is illegal under federal law. So, what has happened instead is that each state government has put its local staff on the task of researching chemistry regulations and drafting a series of requirements that is modeled on federal standards but is authored by the state legislature and enforced with state authority exclusively. This scenario creates a regulatory patchwork where each state has slightly different versions of similar requirements and enforces them differently.

One such state is Nevada. Back in 2015, the state's Department of Public and Behavioral Health used the code of federal regulations to find action levels for pesticides in cannabis. Because the Nevada departments did not feel they had sufficient medical authority to actually make that determination, even in the form of citing the most appropriate example in a comparable industry, they went with a policy of using the lowest stated limit for any food item in the CFR as the level for cannabis, guaranteeing they were not setting a higher limit than would be warranted. Although many changes have happened to Nevada regulations since then, this was the process of authoring analytical chemistry regulations for the state licensed cannabis program.

The state of California, which began the same process two years later in 2017, had significantly more resources at the state and community level. Meetings were called for public input on proposed regulations and committees were formed with scientists and doctors who were familiar with analytical chemistry regulation. The levels and tests being set seemed more reasonable and to be authored by a more informed community of professionals and volunteers, and so a big improvement over the counter example of

	LOD (% w/w)	0.0055	0.0050	0.0093	0.0075	0.0073	0.0077	0.0075	0.0088	0.0080	0.0071	0.0076
	LOQ (% w/w)	0.0504	0.0460	0.0851	0.0688	0.0674	0.0704	0.0692	0.0812	0.0734	0.0649	0.0695
Sample Name		**CBDV %**	**CBDA %**	**CBGA %**	**CBG %**	**CBD %**	**THCV %**	**CBN %**	**d9-THC %**	**d8-THC %**	**CBC %**	**THCA %**
PB - Prep blank		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
MB - Matrix blank		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
LCS - Lab Control Standard		<LOQ	<LOQ	<LOQ	<LOQ	98.84%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
LRS - Lab Replicate Sample		<LOQ	<LOQ	<LOQ	<LOQ	4.49%	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
ICV - Indepdent Cal Verification		91.78%	101.73%	100.00%	101.07%	100.04%	105.27%	99.65%	97.11%	98.31%	103.74%	101.70%
Sample 01 10X		ND	<LOQ	12.59	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.13
Sample 02 10X		ND	<LOQ	12.39	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.11
Sample 03 10X		ND	<LOQ	11.37	<LOQ	ND	ND	ND	ND	ND	<LOQ	0.13
Sample 04 10X		ND	0.17	8.84	0.07	<LOQ	ND	ND	ND	ND	<LOQ	0.13
Sample 05 10X		<LOQ	9.13	0.42	0.11	2.17	<LOQ	ND	0.18	ND	0.27	0.21
Sample 01 200X		ND	ND	13.17	ND	ND	ND	ND	ND	ND	<LOQ	ND
Sample 02 200X		ND	ND	13.04	ND	ND	ND	ND	ND	ND	ND	ND
Sample 03 200X		ND	ND	12.28	ND	ND	ND	ND	ND	ND	ND	ND
Sample 04 200X		ND	ND	9.30	ND	ND	ND	ND	ND	ND	ND	ND
Sample 05 200X		ND	9.75	ND	ND	2.17	ND	ND	ND	ND	ND	<LOQ
CCV 50ppm		100.20%	100.34%	100.25%	99.68%	100.48%	100.62%	100.84%	100.87%	102.33%	101.07%	101.02%
CCB		<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

Imageπ – A reproduction of a certificate of analysis (CoA) reporting on 11 cannabinoids, with quality control (QC) samples indicated in **green**. The green rows are known QC checks that help rule out the possibility of reporting errors by the lab. Image credit: Digamma.

Nevada was forecast. Many issues came out with enforcement and administration, the role of the then Bureau of Cannabis Control and now the Department of Cannabis Control (DCC) of California. The department had a high turnover of employees and turnaround of applications, and many of the staff were young and inexperienced and the office seemed understaffed to serve the size of the industry in California. Additionally, although conversations were well informed and fluid with the PhDs and MDs in the 2017 committees, by 2019 the enforcement of written codes and regulations were enforced according to department (or bureau) policy.

As different states issue their own testing regulations for state-licensed cannabis labs, different jurisdictions may have very different testing requirements. Although all states have amended their regulations over time to converge on an approximation of federal standards, some states skipped pesticide testing, some skipped microbiological testing, some had no heavy metal requirements, and other saw residual solvents as a test conditional on the solvents disclosed by the operator. But as the states begin to converge on standard cannabis testing regulations, a model that incorporates all solvents, pesticides, metals, and micro-contaminant assays is slowly emerging. The list of analytes, sometimes called the monitoring list, varies significantly between states but has been converging with amendments over time, much like the tests required in each state are converging. A summary of state and federal testing requirements has been shown in Imageρ.

Notice that in the federal requirements right now, only cannabinoid analysis is a requirement, along with moisture because of the fact that the Farm Bill stated the 0.3% Δ9-THC limit on a dry weight basis, so moisture will need to be known in hemp samples to give final results on a dry weight basis. Other than this, all the other requirements that apply to state-licensed cannabis labs do not apply to federal hemp labs, and so the consumers of federal hemp products are without the safety screening that is standard in state programs.

	Potency			Contaminants			
	Cannabinoids	Terpenes	Moisture	Solvents	Pesticides	Metals	Micro
State Labs	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
Federal Labs	TRUE		TRUE				

Imageρ – A chart showing the analyses performed by cannabis analysis labs across states. Notice that federal labs are only required to test cannabinoids and moisture, making them a significantly less resource-intensive operation to establish than state-licensed cannabis labs. Image credit: Digamma.

		State Labs	Federal Labs
Potency	Cannabinoids	$20,000.00	$20,000.00
	Terpenes	$30,000.00	
	Moisture	$1,000.00	$1,000.00
Contaminants	Solvents	$50,000.00	
	Pesticides	$200,000.00	
	Metals	$65,000.00	
	Micro	$12,000.00	
	Total	**$378,000.00**	**$21,000.00**

Imageσ – A chart showing the relative costs of the median cost of used equipment as a comparison between the requirements on capital investment. Notice that the retail prices of new equipment would be between three to five times higher. Image credit: Digamma.

This puts consumers of federal hemp products at risk of contamination in their supply chain that is not possible from state-run dispensaries. This is a major safety concern for the public which the public may not be aware of.

There are additional factors that affect patient or consumer safety which are not applicable to medical and recreational cannabis at the state level. We covered these chemical reactions in the chemistry section; they were called Lewis acids. The catalysts that help turn the delta series into HHC were platinum or palladium metal catalyst fused with activated carbon. Both of these reagents are toxic to human health and are traditionally used by large pharmaceutical or other chemical process plants, which have strict protocols for removal and residual monitoring. At the moment, the recreational hemp market has no checks in place other than those voluntarily paid for at operator expense. These products that are being smoked and ingested by consumers may have small or even large amounts of residual toxic catalysts in them that reach the consumer and have negative consequences on their health. Federal safety tests could include many common catalytic reagents that may be present at residual levels in the final product.

In addition to the concerns for public health, there are also concerns about free market and fair play principles. When we look at the median cost of used equipment and compare the approximate cost of starting a state cannabis lab and a federal hemp lab, the cost is over 10 times higher for a state lab. With 10 times higher costs, these labs are caught in a small state market due to the ban on inter-state commerce. Federal hemp products, however, are legal in all 50 states, allowing distribution on a much wider market. When these factors are combined with the higher tax penalties the state cannabis operators have to contend with, the gap in fair play between state cannabis and federal hemp operators is pretty wide at the moment.

CONCLUSION

As the FDA policy and commentary has made clear, it is taking a position of advising extreme caution among the public in using recreational hemp products like the delta series and HHC. Unlike the legal gray zone with CBD years earlier, these compounds are clearly psychoactive and their unregulated widespread distribution would be a broad public health crisis. The FDA has a more long-term nebulous stance on CBD, with bizarre exceptions like rescheduling the Epidiolex oral spray formulation as a Schedule V substance while keeping CBD itself in a nebulous state between being a Schedule I component of marijuana and being unscheduled through the Farm Bill. The FDA is likely to take more rapid action to regulate the recreational hemp cannabinoids than it has taken on CBD.

But FDA involvement may not be negative for the fate of these cannabinoids, even if it may remove them from the recreational hemp phenomenon. If any of these structures or their derivatives show improved efficacy in treating conditions over traditional medicines, they could be scheduled in the FDA system and be made available through prescriptions. Conversely, the opposite of this effect could happen and follow the "spice" products that use fully synthetic cannabinoids, many of which have toxic properties not present in the natural cannabinoids. These products caused a lot of overdoses and emergency room visits about ten years ago, before many of the more dangerous compounds being used in them were banned by federal authorities, as well as a series of bans from state governments such as Kentucky, Texas, and Florida. So, the fate of FDA involvement with this current phenomenon is still very uncertain.

The implementation of contaminant tests, which would most likely need to be at the federal level, would most likely not come out of FDA scheduling as the process for studying and evaluating a potential drug is well defined and would not follow the organic growth of testing regulations as was seen in the state medical and recreational cannabis programs. It is possible that the USDA or another agency that has more lax supply chain policies may implement some sort of standards of both potency and contaminants, including contaminants specific to the semi-synthetic cannabinoids and their catalysts.

Nearly everyone watching the recreational hemp phenomenon is predicting that the current status quo cannot last long. But as a large industry is growing around these compounds and is in direct competition with the state licensed cannabis operators, federal lawmakers may find themselves between two difficult choices. One is to continue to allow the state cannabis industries to be undercut, and the other is to allow federal progress and doom the new industries that have grown nationally to vanish overnight. Regardless of the outcome, a change is almost certainly coming soon.