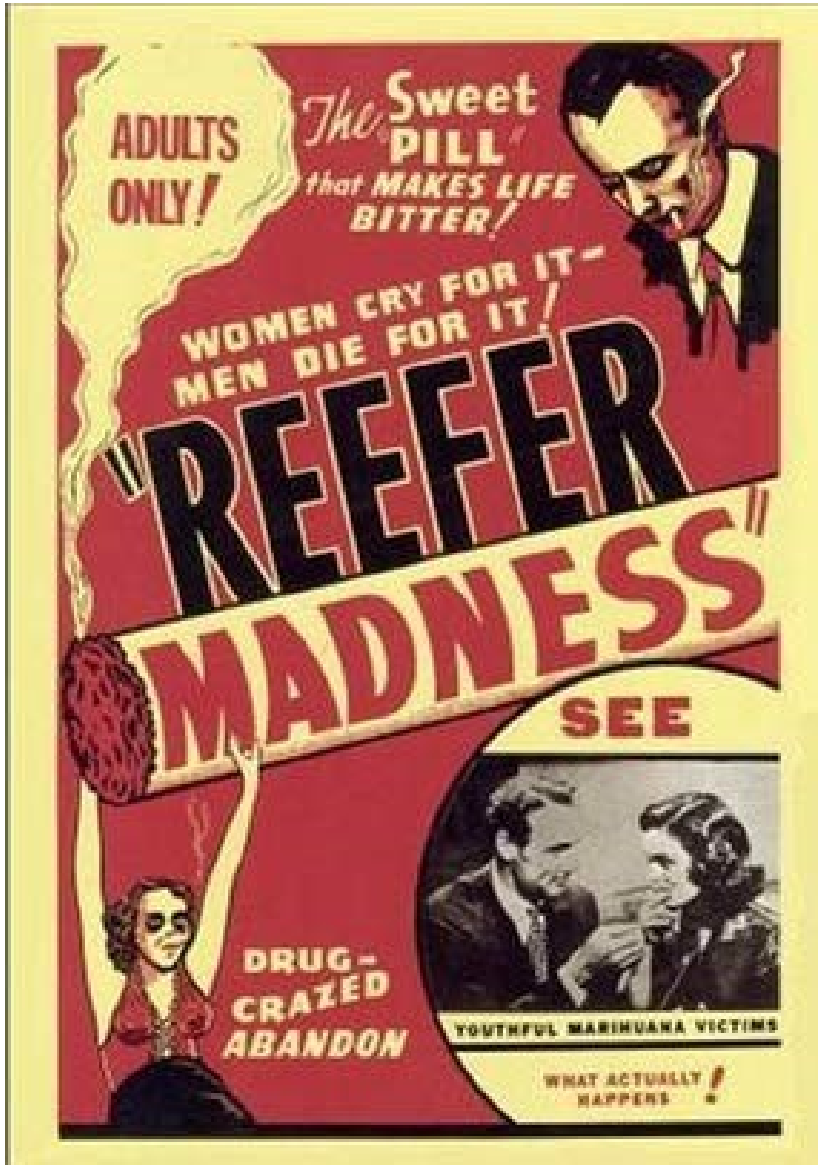
Overview and Update on Cannabis Regulations

Claire Kruger, PhD
ChromaDex Spherix Consulting
ClaireK@chromadex.com

Regulation of *Cannabis sativa L.*



Cannabis sativa L.

- Hemp vs. Marijuana
- Cannabis, cannabis-derived compounds
  - Cannabidiol and THC
- Dietary Supplements
- Generally Recognized As Safe Ingredients
- Medical marijuana
- Recreational marijuana
- Drugs

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Cannabis sativa L.

- To date, over 100 phytocannabinoids have been identified.
  - The major phytocannabinoids are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are derived from the precursor cannabigerol (CBG).

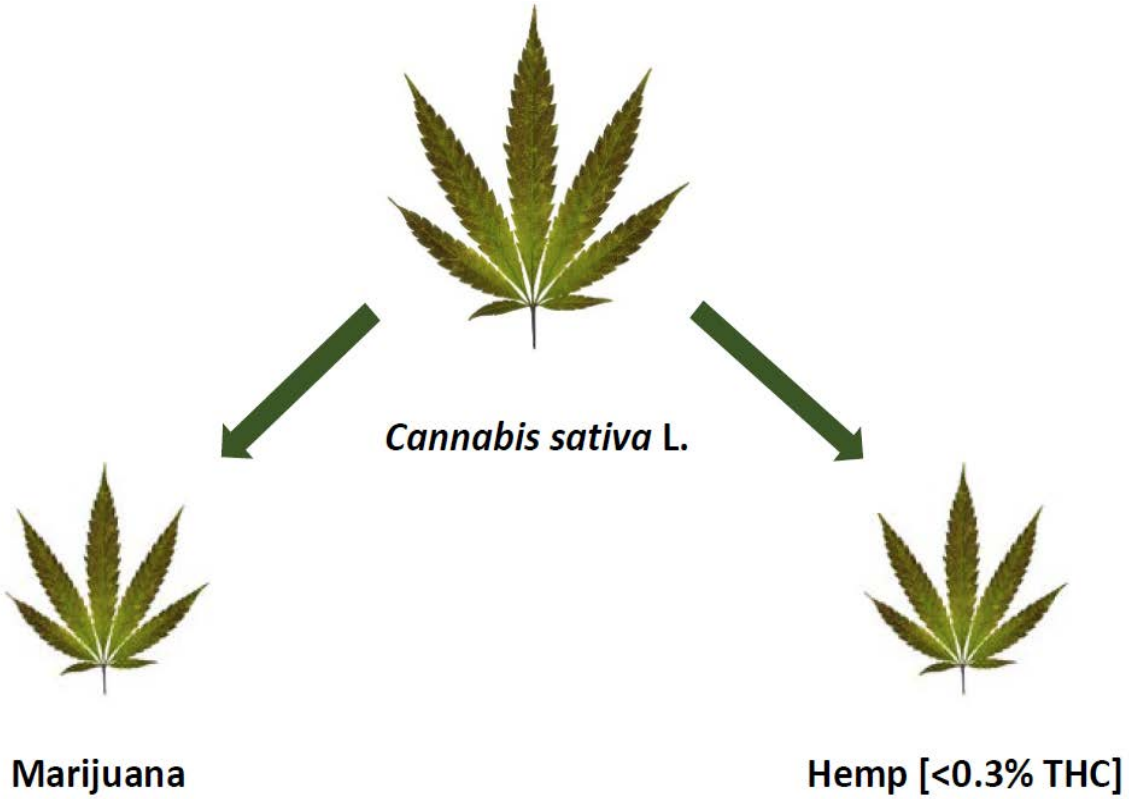
https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Agriculture Improvement Act of 2018

- 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 Δ^9-tetrahydrocannabinol (THC) concentration of not more than 0.3 percent on a dry weight basis.
- Law changes certain federal authorities relating to the production and marketing of hemp, defined as cannabis (*Cannabis sativa L.*) and derivatives of cannabis with "extremely low" (less than 0.3 percent on a dry weight basis) concentrations of the psychoactive compound (THC).
- Includes removing hemp from the Controlled Substances Act which means it is no longer an illegal substance under federal law.

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Hemp vs. Marijuana



- Hemp cultivars of *Cannabis sativa*) contain NMT 0.3 percent (dry weight) of THC (Δ^9-tetrahydrocannabinol)
- Marijuana cultivars of *Cannabis,* not categorized as hemp based on above definition, are classified as schedule I

www.ahpa.org
Accessed December 20, 2018

Agriculture Improvement Act of 2018

- Drug Enforcement Agency no longer has authority over hemp cultivation or hemp-containing products
- Hemp cultivation now lawful within the US; states must establish and maintain hemp "plan" to the USDA
- Hemp ingredients now permitted in food, dietary supplements, cosmetics and personal care products…all subject to relevant regulations (e.g., cGMPs, labeling, safety (e.g., GRAS, NDI); (no longer under Controlled Substance Act 1970)

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Agriculture Improvement Act of 2018

- What didn't change:
  - FDA still regulates products containing cannabis or cannabis-derived compounds under FD&C Act and section 351 of the Public Health Service.
  - FDA treats products containing cannabis or cannabis-derived compounds as they do any other FDA-regulated products — meaning they're subject to the same authorities and requirements as FDA-regulated products containing any other substance. This is true regardless of the source of the substance, including whether the substance is derived from a plant that is classified as hemp under the Agriculture Improvement Act.

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Agriculture Improvement Act of 2018

- What didn't change:
  - FDA continues to be concerned at the number of drug claims being made about products not approved by the FDA that claim to contain CBD or other cannabis-derived compounds. Among other things, the FDA requires a cannabis product (hemp-derived or otherwise) that is marketed with a claim of therapeutic benefit, or with any other disease claim, to be approved by the FDA for its intended use before it may be introduced into interstate commerce.

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Agriculture Improvement Act of 2018

- What didn't change:
  - It's unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived. This is because both CBD and THC are active ingredients in FDA-approved drugs and were the subject of substantial clinical investigations before they were marketed as foods or dietary supplements. Under the FD&C Act, it's illegal to introduce drug ingredients like these into the food supply, or to market them as dietary supplements.

https://www.govinfo.gov/content/pkg/BILLS-115hr2enr/pdf/BILLS-115hr2enr.pdf
Updated December 14, 2018; Signed by President Trump, December 20, 2018
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Posted December 20, 2018

Agriculture Improvement Act of 2018

- Pathways for companies to seek approval from FDA to market:
  - Drug Approval: used to make a therapeutic claim
  - Drug Exclusion Rule: for circumstances in which certain cannabis-derived compounds might be permitted in food
  - GRAS: foods derived from parts of the hemp plant that may not contain CBD or THC

Drug Approvals

- The FDA approved Epidiolex (cannabidiol)oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana.
- The FDA has also has approved Marinol and Syndros for therapeutic uses, including for the treatment of anorexia associated with weight loss in AIDS patients. Marinol and Syndros include the active ingredient dronabinol, a synthetic THC which is considered the psychoactive component of marijuana.
- Another FDA-approved drug, Cesamet, contains the active ingredient nabilone, which has a chemical structure similar to THC and is synthetically derived.

Generally Recognized As Safe

Three GRAS notices related to hulled hemp seeds, hemp seed protein and hemp seed oil received no questions regarding the company's conclusion that the use of such products as described in the notices is safe.

FDA "No Questions" on Three Hemp GRAS Notifications

December 20, 2018

The U.S. Food and Drug Administration has completed its evaluation of three generally recognized as safe (GRAS) notices for hemp seed-derived food ingredients. The GRAS notices were submitted by Fresh Hemp Foods, Ltd. The agency has no questions about Fresh Hemp Food's conclusion that the following ingredients are GRAS under their intended conditions of use: hulled hemp seed (GRN765), hemp seed protein powder (GRN771), and hemp seed oil (GRN778).

Foods containing hemp seed and hemp seed-derived ingredients are currently marketed in the US. Hemp seeds are the seeds of the hemp plant, Cannabis sativa. Although hemp is from the same species as cannabis (marijuana), the seeds themselves do not naturally contain tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis. The hemp seed-derived ingredients that are the subject of these GRAS notices contain only trace amounts of THC and CBD, which the seeds may pick up during harvesting and processing when they are in contact with other parts of the plant. Consumption of these hemp seed-derived ingredients is not capable of making consumers "high".

https://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm628910.htm
Posted and Accessed December 20, 2018

Hemp GRAS Notifications

- Specifications for dehulled hemp seed that include limits for THC (≤ 4 mg/kg)
- EDI for THC from all Fresh Hemp Food Products at the 90th percentile is 193.8 µg/person/day
  - This is the level of contamination accepted by FDA as GRAS.
- EFSA (2011) set a provisional maximum tolerable daily intake of 0.4 µg/kg/day or 24 µg/person/day
- FSANZ (2012) established a tolerable daily intake (TDI) of 6 µg/kg/day or 360 µg/person/day
- Important to note that the weakness in these limits are that they are based on subjective self-reported intoxication scales, with application of safety factors from LOAELS identified in clinical studies

Dietary Supplements

Can a product that contains THC or CBD be sold as a dietary supplement?

- NO. FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under sections 201(ff)(3)(B)(i) and (ii) of the FD&C Act, respectively.
  - Under those provisions, if a substance (such as THC or CBD) is an active ingredient in a drug product that has been approved under 21 U.S.C. § 355 (section 505 of the FD&C Act), or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that substance are outside the definition of a dietary supplement.

Drug Exclusion Rule: 21CFR§170.250(c)(1)

"In addition, pathways remain available for the FDA to consider whether there are circumstances in which certain cannabis-derived compounds might be permitted in a food or dietary supplement. Although such products are generally prohibited to be introduced in interstate commerce, the FDA has authority to issue a regulation allowing the use of a pharmaceutical ingredient in a food or dietary supplement. We are taking new steps to evaluate whether we should pursue such a process. However, the FDA would only consider doing so if the agency were able to determine that all other requirements in the FD&C Act are met, including those required for food additives or new dietary ingredients".

Dr. Scott Gottlieb, FDA Commissioner
December 20, 2018

Cannabidiol

- CRN, along with other supplement industry trade associations, wrote to FDA Commissioner Scott Gottlieb, M.D. on Jan. 8 officially requesting a meeting with his office and other relevant FDA personnel to pursue a lawful pathway to market for dietary supplements or foods that contain cannabidiol (CBD) derived from hemp. CRN has received acknowledgment of the agency's receipt of the letter.

The World Health Organization (WHO) 40th Meeting of the Expert Committee on Drug Dependence (June 2018)

- Cannabidiol (CBD)
  - The Committee recommended that preparations considered to be pure CBD should not be scheduled within the International Drug Control Conventions. Based:
    - CBD is one of the naturally occurring cannabinoids found in cannabis plants;
    - There are no case reports of abuse or dependence relating to the use of pure CBD. No public health problems have been associated with CBD use;
    - CBD has been found to be generally well tolerated with a good safety profile. Adverse effects of CBD use include loss of appetite, diarrhea and fatigue;
    - CBD is not specifically listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. However, if prepared as an extract or tincture of cannabis it is controlled in Schedule I of the 1961 Single Convention on Narcotic Drugs;
    - There is no evidence that CBD as a substance is liable to similar abuse and similar ill-effects as the substances in the 1961 or 1971 Conventions such as cannabis or THC, respectively.

https://www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/

Medical Marijuana

- Refers to using the whole, unprocessed marijuana plant or its basic extracts to treat symptoms of illness and other conditions. The U.S. Food and Drug Administration (FDA) has not recognized or approved the marijuana plant as medicine.
- The FDA requires carefully conducted clinical trials to determine the benefits and risks of a possible medication. So far, no NDA has been approved for the use of the marijuana plant (as opposed to its cannabinoid ingredients such as THC and CBD) and so it is unknown if the purported benefits outweigh the potential risks in patients it's meant to treat.
- However, a growing number of states have legalized marijuana for medical use (currently medical marijuana is legal and 33 states and the District of Columbia; several states allow restricted use of medical marijuana).

Medical Marijuana

- At the federal level, marijuana remains classified as a Schedule 1 substance under the controlled Substances Act, where Schedule I substances are considered to have a high potential for dependency and no accepted medical use, making distribution of marijuana a federal offense.
- In October of 2009, the Obama Administration sent a memo to federal prosecutors encouraging them not to prosecute people who distribute marijuana for medical purposes in accordance with state law.
- In late August 2013, the U.S. Department of Justice announced an update to their marijuana enforcement policy. The statement (Cole Memorandum) read that while marijuana remains illegal federally, the US DOJ expects states like Colorado and Washington to create "strong, state-based enforcement efforts.... and will defer the right to challenge their legalization laws at this time." The department also reserves the right to challenge the states at any time they feel it's necessary.

Medical Marijuana

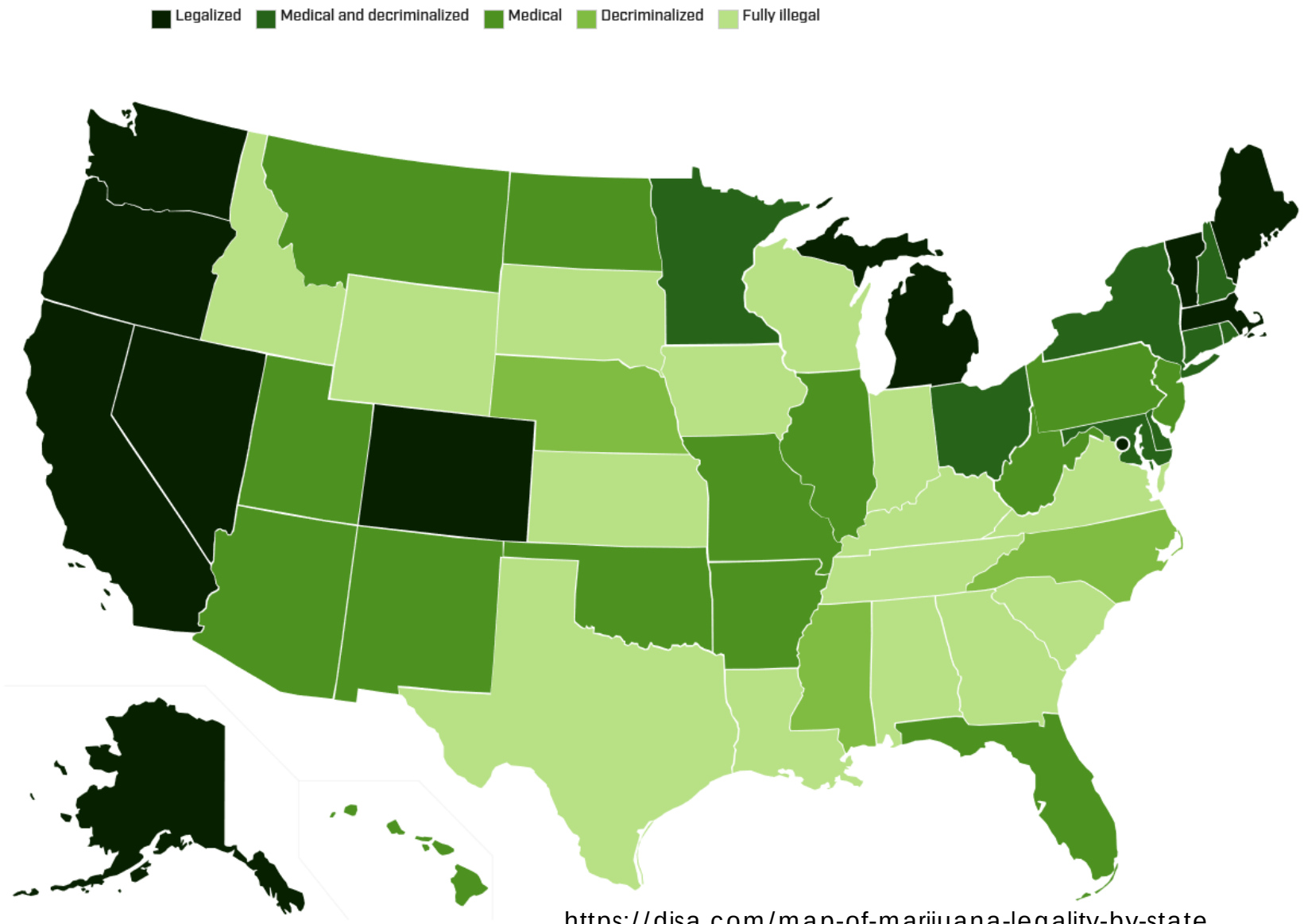
- In January 2018, former Attorney General Sessions issued a Marijuana Enforcement Memorandum that rescinded the Cole Memorandum, and allows federal prosecutors to decide how to prioritize enforcement of federal marijuana laws. Specifically, the Sessions memorandum directs U.S. Attorneys to "weigh all relevant considerations, including federal law enforcement priorities set by the Attorney General, the seriousness of the crime, the deterrent effect of criminal prosecution, and the cumulative impact of particular crimes on the community."

https://www.justice.gov/opa/pr/justice-department-issues-memo-marijuana-enforcement

Recreational Marijuana

- Marijuana prohibition began 80 years ago when the federal government banned the sale, cultivation, and use of the cannabis plant. It remains illegal at the federal level. Overturning prohibition is one of the few hot-button topics with widespread support.
- A recent poll by the Pew Research Center found that 62% of Americans, including 74% of millennials, said they supported legalizing marijuana.
- Ten states and Washington, DC, have now legalized marijuana for recreational use for adults over 21.
- Last year was also a banner year for marijuana legalization globally.
  - Last, October Canada legalized marijuana federally, becoming the first G7 country to do so.
  - Mexico's Supreme Court also ruled that marijuana prohibition is unconstitutional.

Map



https://disa.com/map-of-marijuana-legality-by-state

Thank you!

Claire Kruger, PhD
ChromaDex Spherix Consulting
ClaireK@chromadex.com