The Impact of the Agriculture Improvement Act of 2018 and the Need for a Sound Public Health Path on Cannabinoids

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I want to discuss the growing use of cannabinoids, and in particular, THC and CBD. These are two of the principal active ingredients in cannabis. The 2018 Farm Bill, which legalized the growing of hemp, altered the landscape for CBD.[1] It placed considerations for legalizing CBD's use on a new regulatory path. But the Farm Bill didn't just impact the framework for CBD. It also indirectly influences how we address other active ingredients from cannabis, especially THC. The widespread cultivation and legalization of cannabis and hemp makes these active ingredients more ubiquitous and more likely to be used by consumers. It also heightens the need to confront the risks of these ingredients.

I want to discuss, in turn, how I believe we should approach each of these compounds, starting with THC. While the framework that'll ultimately govern a legal path for proper research and use of these compounds are different, the impetus behind their growing popularity stems from a common political origin borne of state efforts to legalize cannabis.

That political effort is resulting in the widespread recreational use of cannabinoids, and the promotion of their supposed medical benefits. I believe the growing fashion around cannabis requires us to end our political ambivalence when it comes to the proper regulation of these active ingredients, especially Tetrahydrocannabinol or THC. We need a uniform set of federal policies that allow an efficient path for proper research, and guard against the public health consequences that accrue through the whimsical recreational use of potent forms of THC, especially by teenagers and expectant moms.

State laws that've loosened access to cannabinoids have come at a public health cost. Ultimately, a federal regime could make it easier to access cannabis for conducting proper studies to assess the myriad of loose medical claims that are being cited about the purported benefits of cannabinoids. At the same time, a federal regime should tighten permissive state practices that have made it far too easy for recreational marijuana to gain acceptance and for these compounds to get into the hands of kids.

Ultimately, we need to move past the social stigma around cannabis and address these complex public health and regulatory issues objectively. If there's a policy and regulatory framework under which certain products can be properly judged to be safe and effective based on sound scientific review, then we need to support these opportunities for patients. If the science demonstrates that there are risks associated with certain uses, we

[1] Stein, Jeff, Congress just passed an $867 billion farm bill. Here's what's in it. The Washington Post, December 12, 2018, https://www.washingtonpost.com/business/2018/12/11/congresss-billion-farm-bill-is-out-heres-whats-it/

need to restrict the easy access. What we can't do is let the development of an objective process for mediating these questions to be driven by the strong emotions on both sides of the cannabis debate. Our regulatory policy must follow the direction of sound science.

The Food and Drug Administration has always been supportive of responsible research into the active ingredients of cannabis.[2] But marijuana is still a Schedule I compound with known risks.[3] That scheduling reflects proper concerns around the effects of THC. But it also makes it hard to access cannabis for medical research. Studies to evaluate whether marijuana or its components could be safe and effective in the treatment of medical disorders should be more accessible. That also means these compounds should be held to the same standard as other drugs. And certainly, cannabinoids shouldn't be held to a lower standard which, in too many cases, is precisely what's happening today.

Thirty-three states have comprehensive medical marijuana markets, including 11 with full legalization that includes recreational applications.[4] Through these actions, the states have provided an official imprimatur, if not explicit sanction, to sometimes dubious claims that cannabis has utility for a range of medical conditions. The states have implicitly affirmed, in the face of conflicting data, that THC can be used safely for recreation.

Cannabis has been around a long time. There's been plenty of time to develop rigorous science to affirm its purported medicinal benefits. That body of credible and well controlled science is thin. Outside of a few controlled trials and approved uses, the vast majority of medical claims haven't been held up to any widely accepted scientific standard. They'd never meet the threshold for approval by FDA based on the currently available evidence.

It's ironic then, if not unfortunate, that some of the proponents of so-called medical marijuana are also the same people who advocate for tougher standards on ethical pharmaceuticals and stronger FDA oversight of prescription medicines. The latter is appropriate. But the contrived dichotomy between how we treat the active ingredients from cannabinoids and active ingredients from any other source is not. Medical claims that some deem permissible in the context of marijuana wouldn't even get into the door at FDA based on the scientific evidence supporting cannabinoids. There are now two political standards and regulatory expectations – one for the politically fashionable expansion of purportedly medicinal applications of marijuana, and one for everything else.

This dichotomy wouldn't be rational even if marijuana were completely benign. But it's not. Ultimately, this conflict needs to be confronted. FDA has a program that's dedicated

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[2] Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency's continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products, April 2,2019. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation

[3] DEA: Drug Scheduling, https://www.dea.gov/drug-scheduling

[4] Paybarah, Azi, About 160,000 People in New York to See Their Marijuana Convictions Disappear. The New York Times, August 28, 2019. https://www.nytimes.com/2019/08/28/nyregion/marijuana-records-new-york-city.html?rref=collection%2Ftimestopic%2FMarijuana%20and%20Medical%20Marijuana

to supporting the development of drugs derived from plant sources.[5] FDA also has an active program to assist drug developers who want to investigate marijuana and its active components through properly controlled clinical trials.[6] That system works. There are researchers who've filed investigational new drug applications to evaluate the active ingredients from cannabis in properly controlled studies. This framework allows a pathway to demonstrate the potential for safe and effective uses of cannabis. Sponsors can get targeted help from an FDA team to advance development. FDA has already approved three drugs that contain a synthetic version of THC.[7] So any rejection of proper research, and active engagement of the regulatory process, is not for lack of an efficient pathway.

Yet it's also true that the scheduling process and international treaties make it difficult for researchers to get access to high grade cannabis to conduct studies. A sponsor must go through a complex process to register with DEA and obtain research-grade marijuana from a DEA-approved grower.[8] Right now, there's only one facility -- located in Mississippi – that's approved by the federal government to grow marijuana for research purposes.[9]

Many researchers complain that this facility's product is not concentrated enough for effective research. These are addressable challenges. Congress can take specific action to enable easier access to cannabis that's appropriate for medical research. If we believe that cannabis has medicinal potential, we should focus on enabling suitable research rather than bypassing these norms through wholesale legalization. The lenient state laws will actually have the contradictory effect of making proper research more challenging if cannabis is widely accessible in the absence of any prerequisite that it undergo formal studies. Without a requirement for proper research, however, consumers could be left in the dark when it comes to making fully informed decisions about using cannabinoids, and patients could be misled about the relative effectiveness of different therapeutic options.

Without scientific evidence, state policy actions have filled the culture with new attitudes around the risks and benefits of cannabis as well as its patterns of use, impacting public health. In 2017, 26 million Americans aged 12 and older reported using marijuana in the

[5] FDA: Botanical Drug Development: Guidance for Industry, December, 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry

[6] FDA: Marijuana Research with Human Subjects, https://www.fda.gov/news-events/public-health-focus/marijuana-research-human-subjects

[7] FDA Regulation of Cannabis and Cannabis-Derived Products: Questions and Answers, https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers#approved

[8] DEA announces steps necessary to improve access to marijuana research, August 26, 2019. https://www.dea.gov/press-releases/2019/08/26/dea-announces-steps-necessary-improve-access-marijuana-research

[9] Products Supplied by UM to the NIDA Drug Supply Program, The University of Mississippi, https://pharmacy.olemiss.edu/marijuana/products/

past year.[10] This was a nearly 50 percent increase in since 2007.[11] In addition, more than 7,000 people, on average, initiated marijuana use each day in the U.S.[12] Over four million Americans aged 12 and older met the criteria for a cannabis use disorder in 2017.[13]

These trends were present in subsequent surveys. In the 2018 Monitoring the Future Survey, attitudes toward the potential harm from cannabis use fell among teenagers. There's little doubt that state laws legalizing cannabis and policies that tout its purported therapeutic qualities impact the cultural perceptions of cannabinoids and contribute to this perception of safety. In the same survey, around 6 percent of 12th graders continue to report daily use of marijuana. This figure corresponds to about one in 16 high school seniors. Alongside more widespread use of marijuana by kids is also declining concern for the risks from routine use. One in four 12th graders say that regular marijuana use poses a great risk. This is a figure that's less than half of what it was 20 years ago.[14]

Declining concern for its risks and growing permissibility of marijuana -- alongside its easy availability in vapes and other forms -- translate into rising use by minors. Increasingly, kids are using vaping pens to inhale ultra-potent aerosolized forms of marijuana. While past month marijuana vaping is fairly low -- reported by 2.6 percent of 8th graders, 7.0 percent of 10th graders, and 7.5 percent of 12th graders -- these numbers represent respective increases of 59.7 percent, 62.7 percent, and 50.6 percent over 2017 rates.[15]

This is a practice referred to as "dabbing." Vaping marijuana is often done by heating concentrated cannabis oil, called butane hash oil. Dabs contain high concentrations of THC. They can also contain dangerous emulsifying agents, as well as pesticides and fungicides used on the marijuana plant. These chemicals can transform into dangerous substances when superheated in a vaping pen. The quality of the vape pens also vary widely and can heat the extracts at a temperature that may discharge harmful constituents in the liquids. Many thinning agents and flavoring additives have not been safety tested. Cannabis is also sometimes sprayed with the fungicide Eagle 20 or Myclobutanil is a chemical that's stable at room temperature, but releases highly toxic hydrogen cyanide gas if heated past its boiling point of 205°C. As for the hardware used to heat liquids to precise temperatures to improve the safety of what's an inherently harmful endeavor, FDA

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[10] Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health, https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf

[11] Results from the 2007 National Survey on Drug Use and Health: National Findings, https://www.dpft.org/resources/NSDUHresults2007.pdf

[12] Azofeifa, Azofeifa, et al., National Estimates of Marijuana Use and Related Indicators — National Survey on Drug Use and Health, United States, 2002–2014. MMWR Surveill Summ 2016; 65 (No. SS-11):1–25. https://www.cdc.gov/mmwr/volumes/65/ss/ss6511a1.htm

[13] Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health, https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf

[14] National Institute on Drug Abuse, Monitoring the Future Survey: High School and Youth Trends, December 2018. https://www.drugabuse.gov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends

[15] National Institute on Drug Abuse, Monitoring the Future Survey: High School and Youth Trends, December 2018. https://www.drugabuse.gov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends

doesn't regulate a vape pen unless it's intended and promoted for use with nicotine derived from tobacco. That's FDA's legal hook. So, vape pens sold to vaporize THC aren't regulated by FDA, and typically go unregulated by states. In recent months we have seen the national launch[16] of vape pen brands that are marketed for use with THC and CBD.

Sometimes also known as "wax," or "crumble," these vaped concentrates often contain three times more THC than what's in dried marijuana flower. These concentrated products can contain up to 76 percent THC. By comparison, traditional marijuana smoking has THC concentrations around 3 to 5 percent.[17] Yet, data shows that THC concentration in marijuana plants has risen threefold between 1995 and 2014. Other data shows that the THC content of marijuana as detected in confiscated samples over the past 30 years, has steadily rose from about 3 percent in the 1980s to almost 15 percent in 2012.[18]
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Those rightly concerned about the health effects of teenage vaping of nicotine containing e-cigarette products should be equally, if not even more concerned, about the health effects of vaping cannabinoids like THC and CBD. Especially given the risk of oils and other unsafe ingredients being used to emulsify these ingredients in the vape liquids.

It should come as little surprise that the vaping of these cannabinoids has risks, and now seems to be closely linked to a mysterious lung illness that has swept across the country over the past few months, according to the Centers for Disease Control and Prevention.[19] Most of the victims are young people, who've been admitted to hospitals with symptoms that can include severe shortness of breath, fever, vomiting and diarrhea. As many as six deaths have already been associated with these vaping related illnesses.[20,21] Reports from state health departments indicate at least 400 people have been affected.[22] The cases include a heterogeneous collection of pneumonitis patterns that include acute lipoid pneumonia[23], diffuse alveolar damage, and hypersensitivity pneumonitis.[24] Lipoid

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[16] https://www.pax.com/products/pax-3

[17] Office of the Surgeon General, U.S. Surgeon General's Advisory: Marijuana Use and the Developing Brain, https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html

[18] Marijuana far more potent than it used to be, tests find, CBS News, March 23, 2015, https://www.cbsnews.com/news/marijuana-far-more-potent-than-it-used-to-be-tests-find/

[19] Center for Disease Control and Prevention, Severe Pulmonary Disease Associated with Using E-Cigarette Products, August 30, 2019, https://emergency.cdc.gov/han/han00421.asp

[20] Thayer, Katie, An Illinois resident just died after a mysterious vaping-related illness. It could be the first death linked to vaping in the U.S. The Chicago Tribune, August 23, 2019. https://www.chicagotribune.com/lifestyles/ct-life-vaping-illness-death-illinois-tt-0823-20190823-s27xqukusfdi7edxjpt6k5e23e-story.html

[21] Abbott, Brianna, What We Know About Vaping-Related Lung Illness. The Wall Street Journal, September 13, 2019. https://www.wsj.com/articles/what-we-know-about-vaping-related-lung-illness-11568194202

[22] Michigan bans flavored e-cigarettes to curb youth vaping epidemic, NBC, September 4, 2019, https://www.nbcnews.com/health/vaping/michigan-bans-flavored-e-cigarettes-curb-youth-vaping-epidemic-n1049526

[23] Pulmonary Lipid-Laden Macrophages and Vaping. New England Journal of Medicine, September 6, 2019. https://www.nejm.org/doi/full/10.1056/NEJMc1912038?query=recirc_curatedRelated_article

[24] Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report. Jennifer E. Layden, Isaac Ghinai, Ian Pray, et al. New England Journal of Medicine. September 6, 2019. https://www.nejm.org/doi/full/10.1056/NEJMoa1911614?query=recirc_mostViewed_railB_article

pneumonia is an inflammatory response that occurs after someone inhales a fat or oil, suggesting that an oil based emulsifying agent in vapes could be one common culprit.[25]

The symptoms can be severe. Of 53 cases reported in Wisconsin and Illinois, 94 percent of patients were hospitalized, and 32 percent required mechanical ventilation, according to case reports in the New England Journal of Medicine.[26] Federal health authorities issued a warning specifically citing vaping products that contain THC or CBD.[27] It's a notable warning since the bulk of the injuries emerged suddenly, coinciding with a recent surge in popularity of CBD vapes this past summer. A recent study published in the journal Pediatrics analyzed data from nearly 50,000 8th, 10th and 12th graders in Arizona. It found that one-third of participants said they had used marijuana. Nearly a quarter said they had used marijuana concentrates with very high levels of THC at least once.[28]

Nicotine containing e-cigarettes have been widely used for many years. If the legally sold, and widely used e-cigarette brands were a common culprit, more frequent reports of lung injuries should have surfaced sooner and appeared nationally, rather than clustered in smaller regions. As the Wall Street Journal noted, "Health officials think that the majority of cases have occurred within the past several months. It is possible the condition has occurred before and is only now being recognized as related to vaping, but many investigators believe it is likely caused by something new, such as an additive or toxin in products or devices."[29] These correlations don't directly implicate something in CBD or THC vape products. But it's known that certain oils used in some CBD liquids can cause these sorts of lung injuries.[30] These concentrates are growing in popularity.

It's not just the risk of acute injuries to the lung from vaping cannabinoids. The risks also concern the effects that these substances have on other aspects of health.

The well documented potential harms related to its use, especially among children, are absent from most of the public conversations on marijuana policy. Research consistently shows that use of marijuana carries significant risk. The psychoactive effects of marijuana render pleasurable feelings that can lead to continued use. And it's estimated that 9 percent of individuals who try marijuana will eventually become addicted.[31] Regular use

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[25] Abbott, Brianna, What We Know About Vaping-Related Lung Illness. The Wall Street Journal, September 13, 2019, https://www.wsj.com/articles/what-we-know-about-vaping-related-lung-illness-11568194202

[26] Vaping-Induced Lung Injury. David C. Christiani, New England Journal of Medicine. September 6, 2019. https://www.nejm.org/doi/full/10.1056/NEJMe1912032

[27] Press Release: CDC, FDA, States Continue to Investigate Severe Pulmonary Disease Among People Who Use E-cigarettes, August 21, 2019, https://www.cdc.gov/media/releases/2019/s0821-cdc-fda-states-e-cigarettes.html

[28] Ryan, Sheryl et al., Use of Cannabis Concentrates by Adolescents, Pediatrics Sep 2019, 144 (3) e20191256, https://pediatrics.aappublications.org/content/144/3/e20191256

[29] Abbott, Brianna, What We Know About Vaping-Related Lung Illness. The Wall Street Journal. September 13, 2019. https://www.wsj.com/articles/what-we-know-about-vaping-related-lung-illness-11568194202

[30] Kaplan, Sheila, and Matt Richtel, The Mysterious Vaping Illness That's 'Becoming an Epidemic'. The New York Times, August 31, 2019, https://www.nytimes.com/2019/08/31/health/vaping-marijuana-ecigarettes-sickness.html

[31] National Institute on Drug Abuse, Marijuana, July 18, 2019, https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive

of cannabis is also a gateway to other addictions. More than 90 percent of heroin users report a prior history of marijuana use, compared to a prior history of painkiller use.[32]

There are two safe and effective, FDA approved uses of naturally derived CBD for the treatment of rare pediatric seizure disorders. So, there are therapeutic uses for these active ingredients when they're properly studied and delivered in reliable and quality formulations. But the kinds of recreational use among kids that is in question with these state legalization efforts creates a significant risk of harm without any ostensible benefits.

The use of marijuana can also distort perceptions. This can lead to poor judgment and impaired balance and coordination. All of these effects can increase the likelihood of engaging in risky behaviors or can lead to injuries and other health consequences. In addition, regular marijuana use has been shown to impair cognition leading to problems with memory, learning, attention, and concentration. In some studies, there's evidence of permanent impairment in executive function and short-term memory from regular use.[33]

While there's debate related to many of these findings, there's little mistaking the mounting evidence that regular use of cannabinoids carries risks, some perhaps significant. These potential risks are especially concerning for children. The developing brain can be especially susceptible to the effects of THC, which can interfere with neurodevelopment. The endocannabinoid system is present from the beginning of central nervous system development, where it plays an important role in the formation of neural circuitry, including migration of neurons, the outgrowth of their axons and dendrites.[34]

Substances that interfere with this system could affect how the fetal brain grows and wires itself. Yet surveys show that an increasing number of adolescents and pregnant women use the drug, which can be eaten, smoked or vaped. These risks prompted my former colleague, the U.S. Surgeon General Jerome Adams – just this month – to issue a rare public health warning that no amount of THC is safe for teens, young adults and pregnant women. He noted that "While the perceived harm of marijuana is decreasing, the scary truth is that the actual potential for harm is increasing." Adams observed that nearly one in five people who begin marijuana use during adolescence become addicted.[35]

Chronic use of marijuana in adolescence has been linked to declines in IQ scores that don't recover after cessation of marijuana use.[36] One study tracked individuals with varying degrees of marijuana use over time and found that the most persistent marijuana users experienced a 5 to 6 percent decline in IQ scores from the age of 13 to the age of

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[32] Finn, Kenneth. "Why Marijuana Will Not Fix the Opioid Epidemic." Missouri medicine vol. 115,3 (2018): 191-193.
[33] National Institute on Drug Abuse, Marijuana, July 18, 2019, https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive
[34] Ryan, Sheryl et al., Use of Cannabis Concentrates by Adolescents, Pediatrics Sep 2019, 144 (3) e20191256, https://pediatrics.aappublications.org/content/144/3/e20191256
[35] Aubrey, Allison, Surgeon General Sounds Alarm On Risk Of Marijuana Addiction And Harm, August 29, 2019, https://www.npr.org/sections/health-shots/2019/08/29/755423290/surgeon-general-sounds-alarm-on-risk-of-marijuana-addiction-and-harm
[36] Meier, Madeline et al., Persistent cannabis users show neuropsychological decline from childhood to midlife, July 30, 2012. https://www.pnas.org/content/pnas/109/40/E2657.full.pdf

38.[37] Moreover, in addition to impacts on cognition, marijuana use in early adolescence, especially frequent use, is associated with a number of mental health, substance use, and social risk factors. Other reliable studies have revealed similar findings.[38] Marijuana use has also been linked to early onset of psychotic disorders, such as schizophrenia.[39]

Exposure to marijuana during pregnancy can be especially concerning. Use of marijuana in pregnancy has been associated with lower birth weight and increased risk for behavioral problems.[40] In one study, compared to nonuse, an average use of marijuana six or more times per week during pregnancy was associated with a statistically significant reduction of 0.8 weeks in the length of gestation after consideration of the effects of nicotine, alcohol, parity, mother's pre-pregnancy weight, and the sex of the infant.[41] Other studies have found a correlation between regular marijuana use and earlier delivery.[42]

The harms related with marijuana use are not limited to adolescent exposure. In fact, as rates of marijuana use among adults have risen sharply over the past decade[43] – a time when attitudes about the risks associated with marijuana use have been declining and the state legal landscape has become more conducive to regular marijuana use – so has evidence of risks associated with regular use. Data from SAMHSA's National Survey on Drug Use and Health[44] found marijuana use among people 18 years and older was significantly associated with other drug use, mental health, and social risk factors. Compared to people who've never used marijuana, people who've ever used were at higher risk for having use disorders related to alcohol, cocaine, and other drugs.

Similarly, data suggests these groups were at higher risk for being unemployed, or on probation or parole in the past year. The results consistently showed that the more frequent use group had higher risks for all of the examined outcomes. It's important to point out that most of the long-term effects have been observed among heavy or chronic

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[37] Meier, Madeline et al., Persistent cannabis users show neuropsychological decline from childhood to midlife, July 30, 2012. https://www.pnas.org/content/pnas/109/40/E2657.full.pdf

[38] Center for Disease Control and Prevention, What You Need to Know About Marijuana Use in Teens, https://www.cdc.gov/marijuana/factsheets/teens.htm

[39] Office of the Surgeon General, U.S. Surgeon General's Advisory: Marijuana Use and the Developing Brain, https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html

[40] The American College of Obstetricians and Gynecologists, Marijuana and Pregnancy (Infographic), https://www.acog.org/Patients/FAQs/Marijuana-and-Pregnancy-Infographic?IsMobileSet=false

[41] Marijuana use during pregnancy and decreased length of gestation. P.A. Friedab, B. Watkinsonab, A. Willanab. American Journal of Obstetrics and Gynecology, Volume 150, Issue 1, 1 September 1984, Pages 23-27

[42] Effect of Marijuana Use in Pregnancy on Fetal Growth. Elizabeth E. Hatch, Michael Bracken. American Journal of Epidemiology, Volume 124, Issue 6, December 1986, Pages 986–993. https://academic.oup.com/aje/article-abstract/124/6/986/174585

[43] Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health, https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf

[44] Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health, https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHFFR2017/NSDUHFFR2017.pdf

marijuana users. Confounding factors detract from our ability to demonstrate causality. But the totality of the data should give increasing pause to our cavalier approach to THC.

Of particular concern is a tie between marijuana use and addiction to opioids.

It's been reported that medical cannabis laws are linked to a lower risk of death from opioid overdose.[45] But it's also been observed that it's hard to translate these population-level analyses to individual marijuana-opioid substitutions. Moreover, the patient population being measured by looking at mortality trends is a small percentage of people who may be using medical marijuana in conjunction with, or instead of, opioids.[46]

The evidence, at best, is mixed. In 2017, Colorado had a record number of opioid overdose deaths from any opioid, including heroin. Colorado has had a medical marijuana program since 2001.[47] In one national survey, individuals who had reported marijuana use in early years were significantly more likely report to prescription opioid misuse and to have a prescription opioid use disorder during a subsequent wave of the same survey.

Some argue that cannabis is used in lieu of opioids for the treatment of pain and may be reducing the rate of opioid addiction. Yet, the body of evidence supporting cannabis for pain consists of 28 studies that involved a collective total of 2,454 patients.[48] This is an arguably small body of evidence to support the sweeping assertions sometimes made.

Given these findings related to THC use, the state laws enabling easy access to THC stand in conflict with federal concerns related to addiction, dependence, and public health. We need a consistent approach to addressing these challenges and creating a scientifically valid framework for advancing any potential benefits from cannabis.

Some of these same challenges also surround use of CBD. The political and commercial imperative to address the issues related to CBD is, in some ways, made more immediate as a result of the Agriculture Improvement Act of 2018, also known as the Farm Bill.

When Congress passed this law, it established a category of cannabis from hemp defined as cannabis and cannabis derivatives with extremely low concentrations THC.[49] Congress also removed hemp from the Controlled Substances Act.[50] This means that CBD is no longer a controlled substance under federal law. The widespread trade in legal hemp is going to make it more difficult to enforce against THC. Many of the tools for

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[45] Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000-2015. Livingston MD, Barnett TE, Delcher C, Wagenaar AC. American Journal of Public Health. 2017 Nov; 107(11):1827-1829.
[46] Finn, Kenneth. "Why Marijuana Will Not Fix the Opioid Epidemic." Missouri medicine vol. 115,3 (2018): 191-193.
[47] Finn, Kenneth. "Why Marijuana Will Not Fix the Opioid Epidemic." Missouri medicine vol. 115,3 (2018): 191-193.
[48] Whiting PF. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. Journal of the American Medical Association. 2015;313(24):2456–2473.
[49] United States Department of Agriculture: Hemp and Farm Bill Programs, https://www.farmers.gov/manage/hemp
[50] United States Department of Agriculture, Executive Summary of New Hemp Authorities, May 28, 2019. https://www.ams.usda.gov/sites/default/files/HempExecSumandLegalOpinion.pdf

detecting cannabis that contains high concentrations of THC are confounded by hemp. For example, drug sniffing dogs that hit on THC cannabis will also hit on legal hemp.

One consequence of the growing ubiquity of hemp is that its easy availability makes enforcement against illegal cannabis more challenging. The widespread access to legal CBD also adds to a growing fashion that somehow cannabinoids are safe for widespread use. They're not. THC has significant risks associated with infrequent and especially regular use. And CBD is not a completely benign substance either. When Congress legalized hemp, they explicitly preserved FDA's authority to protect the public health with respect to CBD. This include preserving FDA's authority to regulate CBD-containing products marketed as foods, supplements, drugs, animal foods, and cosmetics.[51]

We're now seeing CBD-containing foods, supplements, drugs, oils, creams, pet foods, and more, available everywhere from small specialty shops to large national retail chains. The market for CBD sales could reach $20 billion by 2025.[52] These products are also being marketed with unproven claims that they can treat serious diseases like cancer and Alzheimer's disease, despite repeated warnings from FDA. Under current law, CBD cannot be legally marketed in food, dietary supplements, or pet food.[53] And to be sold as a drug with drug claims, it needs to come through the new drug approval process. Epidiolex, a purified form of cannabidiol approved in 2018 to treat certain seizure disorders, is the only FDA approved CBD derivative currently on the market that is legally sold as a drug.[54] We know that CBD has therapeutic potential. It needs to be studied in rigorous clinical trials. It may have the potential to treat a range of neurological conditions, and perhaps movement disorders, among other diseases. But its consumer demand and rising sales are largely predicated on false claims and imprudent marketing.

There's simply no reliable evidence to support the broad range of claims that CBD is a wonder drug that can safely treat autoimmune disease, substance abuse disorders, and a whole range of other medical conditions. There's a palpable risk that patients forego proven treatments and proper medical care when they turn to unproven CBD products.

There's also a risk of serious side effects. We know there is a risk of liver toxicity associated with use at high doses. We don't have enough information about the basic safety of CBD to evaluate key issues like overall exposure if a person consumes it from multiple sources, risks associated with long-term use, effects in vulnerable populations, and interactions with other drugs. Currently marketed products may have undeclared

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[51] Testimony of Amy Abernathy, M.D., PhD, Hemp Production and the 2018 Farm Bill, July 25, 2019. https://www.fda.gov/news-events/congressional-testimony/hemp-production-and-2018-farm-bill-07252019

[52] Dorbian, Iris, CBD Market Could Reach $20 Billion By 2024, Says New Study. Forbes, May 30, 2019. https://www.forbes.com/sites/irisdorbian/2019/05/20/cbd-market-could-reach-20-billion-by-2024-says-new-study/#5d89f7d149d0

[53] FDA Regulation of Cannabis and Cannabis-Derived Products: Questions and Answers. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers

[54] FDA News Release: FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy, June 25, 2018. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms

ingredients and impurities, including THC. As we see from the current crisis related to acute lung injury and vaping – which is related in part or large measure to CBD oils that are being inappropriately vaped -- you don't know what you're getting.

When Congress passed the Farm Bill, many expected that it would create a legal path for CBD to be widely sold in food products like dietary supplements. Some farmers say that the CBD oil from hemp is a high margin derivative from that crop. And to make the growing of hemp economically viable, farmers need to be able to extract and sell CBD from hemp. We need a framework that not only differentiates THC from CBD, but one that also creates a safe and legal path to contemplate the addition of CBD to food and dietary supplements.

Under current law, CBD is only permitted to be used in food or dietary supplements if FDA issues a regulation allowing its use. This is a years-long process subject to notice and comment, requiring a substantial amount of scientific data to be submitted to and evaluated by the Agency, to make sure that safety concerns about CBD are addressed.

Given the intense interest in creating a legal path for hemp derived CBD to be sold as a food or dietary supplement, FDA may not have time to employ this traditional process. There may be a more immediate way for the agency to create a legal path to contemplate the addition of CBD to food while still establishing rigorous checks to ensure the safety of products. FDA can still work toward issuing a regulation creating an overarching framework. But in the meantime, the agency can ask manufacturers to make specific submissions to FDA, such as food additive petitions or new dietary ingredient notifications, in order to demonstrate safety and lawfully market their products.

At the same time, FDA could issue an enforcement discretion policy that allows certain CBD products to remain on the market so long as sponsors are pursuing these petitions in good faith. These products would be subject to stringent conditions aimed at cleaning up the marketplace for CBD and forcing manufacturers to behave more responsibly. Conditional enforcement discretion should address the safety concerns about CBD and help the FDA get the data it needs to conduct a proper scientific evaluation of CBD in foods and supplements. While this process plays out, the FDA could continue to take case-by-case enforcement actions against the bad actors marketing CBD products with unproven claims to treat serious conditions like diabetes, cancer, and Alzheimer's.

Such an approach should also preserve the incentives for drug development and clinical research into CBD for therapeutic purposes. Conditional enforcement discretion could be used to spur the submission of data to FDA and bring CBD in line with other ingredients added to food or contained in dietary supplements. Manufacturers that continue to market CBD-containing products should have to make the required regulatory submission to the FDA within a specified timeframe in order to remain on the market.

Under such a policy, manufacturers could be given a set time period to submit a food additive petition containing information about the physical, chemical, and biological properties of their CBD products and the toxicity studies that the FDA needs to properly evaluate the safety of CBD in food. They'd need to show that their CBD product will

reasonably be expected to be safe according to the labeled uses for the product. Right now, responsible supplement and food manufacturers—those waiting for the FDA and other regulators like the USDA to address the legal and safety considerations before launching products—are being eclipsed by the unscrupulous purveyors of CBD products.

In setting forth a formal policy of enforcement discretion, FDA could make clear that any CBD product remaining on the market subject to enforcement discretion while submissions are prepared and reviewed, can't make any claims to treat disease. Other claims about CBD, for example that it might help with relaxation, should be substantiated with appropriate evidence. In tackling the continued marketing of CBD head on, FDA could enforce compliance with traceability and good manufacturing practice, which would help address concerns about undeclared ingredients and the presence of THC.

This approach could set forth a series of regulatory gates to promote more responsible development and marketing, stop the bad actors preying on vulnerable consumers, and accelerate the process for science-based rulemaking. FDA's policy in this space could be time-limited. Regulatory submissions would have to be pursued in good faith in order for manufacturers to continue to market CBD-containing products. Pushing the industry to collect and submit data to support the potential use of CBD as a food additive or dietary supplement could support the regulatory process and help establish the stable marketplace for hemp-derived CBD envisioned by supporters of the 2018 legislation. An enforcement discretion policy conditioned on robust and timely regulatory submissions would also promote efficient use of FDA enforcement resources to protect consumers.

Finally, for those who want to make drug claims with CBD -- or for that matter, with THC -- FDA already has a well-defined path. These compounds should be subject to the same standards as any other active pharmaceutical ingredient. The political ambivalence that's created two drug regulatory schemes in this country – one for the derivatives of cannabis and one for everything else – must end. Marijuana isn't a special case. We have a well-defined system for regulating active ingredients that are intended to treat disease. We should respect those well-established rules. They've served patients and consumers well.

That pathway includes a requirement for a robust clinical development program, along with careful scientific review through the FDA's drug approval process. This is the most appropriate way to bring beneficial new treatments to patients. This process also includes a review of a new drug's purity and manufacturing controls. Before a high-quality drug can be developed, evaluated, and eventually approved by FDA, the necessary work must be done to identify drugs of potential medical benefit, and conduct rigorous scientific research though adequate and well-controlled clinical trials to demonstrates benefits and risks. This is true for all drugs. It should be true for those derived from marijuana.

Ultimately, we need to better address a legal pathway for active ingredients in cannabis. We also need to be honest and clear about the risks associated with CBD, as well as THC, and the dangers created by our continued ambivalence that's allowed THC containing products to be sold and promoted for inappropriate recreational and

purportedly medical uses. The current federal regime makes proper research too hard. The current state regimes make access – particularly by children – far too permissive.

We need to end the handwringing when it comes to cannabis. We need to firm up regulation over the frivolous recreational uses and make legitimate development of proposed medical applications easier to pursue through proper research. We need to contemplate a federal regime for THC that would enable it to be more easily studied in properly controlled settings for its purported medical uses, while superseding state laws that allow frivolous recreational uses that are creating long-term consequences for adults but especially children. We need a federal reckoning when it comes to cannabis. State action has gotten so far down field while the feds sat on the sidelines; there's no turning back to a time before the states started to pass their lenient laws. There's a need to adopt a uniform national approach to THC that protects consumers. It needs to be rigorous and science based. The vaping injuries show the consequences of what happens when hype gets ahead of science and safe regulation. There's certainly no public health imperative that we as a nation must fully embrace what the states have done, and the risks they've sown.