

# Project CBD

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Comments on the Food and Drug Administration's Request for Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds

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## INTRODUCTION

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Project CBD is a California-based educational nonprofit that reports on developments in cannabis science and therapeutics. Founded in 2010, Project CBD was instrumental in introducing cannabidiol (CBD) to the medical cannabis community in California. Interest in CBD spread from that community to become the hugely popular cultural phenomenon that it is today.

Subject to little manufacturing oversight, the unregulated CBD market thrives in a peculiar legal environment. The CBD molecule is currently both legal and illegal, depending on its botanical source. The 2018 Farm Bill explicitly removed hemp and its derivatives, including CBD, from the list of Controlled Substances and the purview of the Drug Enforcement Administration. (DEA). Consequently, it became the Food and Drug Administration's job to regulate CBD commerce.

But CBD oil derived from cannabis with over 0.3 percent tetrahydrocannabinol (THC) remains a controlled Schedule I substance under federal law and is, therefore, still subject to DEA enforcement. To complicate matters even further, single-molecule CBD is also an FDA-approved Schedule IV pharmaceutical (Epidiolex). CBD's simultaneous status as the most and least restricted class of drug is emblematic of the contradictions within cannabis policy.

Legal ambiguities aside, public enthusiasm for CBD is driving the multibillion-dollar "green rush."<sup>1</sup> Over 64 million Americans have reportedly used a CBD product,<sup>2</sup> many of them for conditions that were unresponsive to conventional therapies. Although the FDA has the authority to crack down on non-pharmaceutical CBD products, thus far it has utilized this authority only sparingly. The limited FDA enforcement policy is in part a reflection of the growing economic and political clout of the cannabis sector. The FDA can't scale with the magnitude of this cultural groundswell. It can't put the CBD genie back in the bottle even if it wanted to.

Several factors have aligned in favor of the present-day CBD surge. It comes at a time of widespread disaffection with a broken, overpriced health care system.<sup>3</sup> Although the mainstream embrace of CBD has all the signs of a fad, it's also driven by a hunger for alternatives to severe pharmaceuticals, a sincere desire for medicine more in synch with natural processes.<sup>4</sup> For some who are struggling with serious illness, artisanal CBD-rich oil is a last-ditch Hail Mary pass. For many others, it is a tonic for coping with endemic despair in a country where substance abuse, depression, and suicide rates are at an all-time high.

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<sup>1</sup> Brangham, William. "What Has Changed in States That Have Legalized Marijuana -- and What Hasn't." *PBS*, Public Broadcasting Service, 9 July 2019, [www.pbs.org/newshour/show/what-has-changed-in-states-that-have-legalized-marijuana-and-what-hasnt](http://www.pbs.org/newshour/show/what-has-changed-in-states-that-have-legalized-marijuana-and-what-hasnt).

<sup>2</sup> Gill, Lisa L. "CBD Goes Mainstream." *Consumer Reports*, 11 Apr. 2019, [www.consumerreports.org/cbd/cbd-goes-mainstream/](http://www.consumerreports.org/cbd/cbd-goes-mainstream/).

<sup>3</sup> Jones, Jeffrey M., and RJ Reinhart. "Americans Remain Dissatisfied With Healthcare Costs." *Gallup.com*, Gallup, 10 Dec. 2018, [news.gallup.com/poll/245054/americans-remain-dissatisfied-healthcare-costs.aspx](https://news.gallup.com/poll/245054/americans-remain-dissatisfied-healthcare-costs.aspx).

<sup>4</sup> Corroon, James M Jr et al. "Cannabis as a substitute for prescription drugs - a cross-sectional study." *Journal of pain research* vol. 10 989-998. 2 May. 2017, doi:10.2147/JPR.S134330

## PRIORITIZING PUBLIC HEALTH

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We are in dire circumstances. Given the scope of the staggering scope of the opioid epidemic, the unmet needs of many struggling with pain and mental health issues, and popular pressure from the massive CBD economy, business-as-usual with respect to regulating CBD is not a viable path forward for the FDA. There's no precedent for regulating a substance that's at once a pharmaceutical, a wellness nutraceutical, an essential oil extract, and an herbal preparation that can be inhaled, ingested, imbibed, or applied topically.

The FDA, however, only recognizes the medical utility of isolated components of cannabis. Single-molecule CBD and single-molecule tetrahydrocannabinol (THC) are both FDA-approved prescription pharmaceuticals. But herbal cannabis, the natural source of CBD and THC, isn't an FDA-approved therapy, and any cannabis plant (or derivative) with more than 0.3 percent tetrahydrocannabinol (THC) remains a federally illegal Schedule I substance, which, by definition, can't have medical value.

There are occasions when public health priorities and pharmaceutical prerogatives are not equivalent. We believe this is the case with CBD and cannabis. We urge the FDA to prioritize public health over private interests, and to steadfastly maintain this focus at the core of its decision-making process.

Extensive preclinical research has shown that CBD is a safe, non-intoxicating, anti-addictive, neuroprotective antioxidant.<sup>5,6,7</sup> Given CBD's intrinsic, low-risk profile and many potential benefits, it should be legally available in many forms without a prescription. Sensible regulations can ensure CBD product safety without going through expensive, time-consuming clinical trials. The goal should be easy public access to diverse CBD-rich product options – pharmaceutical, nutraceutical, and artisanal – that are subject to rigorous manufacturing and compliance oversight.

Concerns that non-pharmaceutical CBD commerce will undermine drug development initiatives are misplaced. Artisanal CBD won't disincentivize clinical pharmaceutical development; if anything, the opposite has proven to be the case. Artisanal cannabis has inspired pharmaceutical innovation. Charlotte's Web, an artisanal, whole plant, CBD-rich hemp oil, was featured as a miraculous anti-seizure remedy on CNN in 2013. Five years later, the FDA approved Epidiolex, a pharmaceutical CBD isolate, for refractory pediatric epilepsy.

Pharmaceutical researchers are already developing synthetic compounds that target the endocannabinoid system for therapeutic benefit.<sup>8</sup> Some of these compounds activate or block or otherwise modulate the same cannabinoid receptors in the brain and body that respond to THC and other cannabis components. Medical scientists are also experimenting with endocannabinoid reuptake

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<sup>5</sup> National Institute on Drug Abuse. "Researching Marijuana for Therapeutic Purposes: The Potential Promise of Cannabidiol (CBD)." NIDA, 20 July 2015, [www.drugabuse.gov/about-nida/noras-blog/2015/07/researching-marijuana-therapeutic-purposes-potential-promise-cannabidiol-cbd](http://www.drugabuse.gov/about-nida/noras-blog/2015/07/researching-marijuana-therapeutic-purposes-potential-promise-cannabidiol-cbd).

<sup>6</sup> Mateus Machado Bergamaschi, Regina Helena Costa Queiroz, Antonio Waldo Zuardi and Jose Alexandre S. Crippa, "Safety and Side Effects of Cannabidiol, a Cannabis sativa Constituent", *Current Drug Safety* (2011) 6: 237. <https://doi.org/10.2174/157488611798280924>

<sup>7</sup> Kerstin Iffland and Franjo Grotenhermen. "An Update on Safety and side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal studies." *Cannabis and Cannabinoid Research*. Dec 2017. <http://doi.org/10.1089/can.2016.0034>

<sup>8</sup> "ICRS 2019 Programme & Abstracts." *International Cannabinoid Research Summit*, International Cannabinoid Research Society, 2019, [www.icrs.co/SYMPOSIUM.2019/ICRS2019.PROGRAMME&ABSTRACTS.pdf](http://www.icrs.co/SYMPOSIUM.2019/ICRS2019.PROGRAMME&ABSTRACTS.pdf).

inhibitors and other compounds that are designed to improve “endocannabinoid tone” without binding directly to cannabinoid receptors. The slow pace of drug development in these areas since the discovery of the cannabinoid receptor type 1 (CB1) thirty years ago cannot be attributed to public (albeit illegal) availability of CBD and cannabis.

## WHOLE PLANT AND ISOLATED CBD

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While favoring single-molecule therapies and the pharmaceuticalization of individual cannabis components, federal policy has stymied clinical research that could validate the therapeutic use of herbal cannabis and its full-spectrum derivatives. Prohibitionists rely on this artificial gap in clinically relevant research to argue that there’s insufficient proof that cannabis is truly a disease modifier. Cannabis flower, with few exceptions, is still forbidden territory for medical scientists. Because of cannabis prohibition and consequent research restrictions, few rigorous probes have analyzed the therapeutic impact of whole plant cannabis extract, and fewer still have compared the results with single-molecule outcomes.

A noteworthy exception is a groundbreaking 2015 Israeli [study](#), which documented the superior therapeutic properties of whole plant CBD-rich cannabis extract as compared to single-molecule CBD in an animal model of pain and inflammation.<sup>9</sup> Both CBD alone and the full spectrum CBD-rich oil had measurable anti-inflammatory and analgesic effects. CBD isolate, however, required a very high and precise dose to be effective, whereas the whole plant extract had a broader therapeutic window and worked well at much lower doses.

“A lot of research has been made to isolate and characterize isolated single constituents of traditional herbal medicine to find their rationale for therapeutic uses,” the Israeli report concluded. “However, our data together with those of others provide legitimation to introduce a new generation of phytopharmaceuticals to treat diseases that have hitherto been treated using synthetic drugs alone. The therapeutic synergy observed with plant extracts results in the requirement for a lower amount of active components, with consequent reduced adverse effects.”

## THERAPEUTIC SYNERGY

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In June 2018, Spanish researchers documented the greater potency and superior efficacy of a full spectrum THC-rich cannabis oil extract compared to single-molecule THC in a preclinical breast cancer study.<sup>10</sup> Both single-molecule THC and full-spectrum THC-rich cannabis oil were shown to have antitumor properties, but the full-spectrum oil performed better than the THC isolate in vitro and in animal models of three different breast cancer subtypes. The Spanish scientists also found positive synergistic effects between the standard chemotherapy drugs and either formulation of THC.

A small but growing body of clinical data formed the basis of a September 2018 meta-analysis by Brazilian scientists, who determined that whole plant CBD-rich extracts are as effective as CBD isolates, if not more

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<sup>9</sup> Gallily, Ruth, et al. “Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol.” *Pharmacology & Pharmacy*, vol. 06, no. 02, 10 Feb. 2015, pp. 75–85., doi:10.4236/pp.2015.62010.

<sup>10</sup> Blasco-Benito S, et al. “Appraising the “entourage effect”: Antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer,” *Biochemical Pharmacology*, Volume 157, 2018, Pages 285-293, ISSN 0006-2952, <https://doi.org/10.1016/j.bcp.2018.06.025>.

so, in treating refractory seizure disorders.<sup>11</sup> Perhaps the most striking conclusion of this study was the dramatic difference in doses required for isolates compared to full spectrum CBD-rich oil extracts. The mean dosage for epileptics using pure CBD was 25.3 mg/kg/day, but for CBD-rich extracts it was 6.0 mg/kg/day.

In other words, CBD in a whole plant extract was over 4 times more potent than pure CBD. Whole plant CBD was also associated with fewer side effects than single-molecule CBD formulations – probably due to the lower dose of CBD required when administered as a whole-plant extract.

Regulatory policy that prioritizes public health should not privilege isolates over full-spectrum cannabis remedies. Single-molecule and full-spectrum CBD can both be highly effective therapies for a number of conditions. Citizens are best served by having access to a wide range of well-regulated, cannabinoid-based product options.

## REAL WORLD DATA

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There's an abundance of anecdotal and survey-based evidence that doctors and dispensaries have accumulated over the years in states where medical cannabis is available through licensed dispensaries or elsewhere via the unregulated black market.<sup>12,13,14,15</sup> The significance of this real-world CBD evidence should not be discounted just because it doesn't meet the gold standard of double-blind, randomized clinical trials, which don't always reflect real-world outcomes.

The gold standard might be optimal for assessing single-molecule pharmaceutical interventions aimed at single, primary outcomes. But that standard cannot account for the complex interplay between cannabis components and the endocannabinoid system. By acting as receptor agonists and antagonists, reuptake inhibitors, and allosteric modulators, CBD and other plant cannabinoids elicit many effects that combine synergistically.

Double-blind randomized clinical trials, while clearly important, aren't the only way – and might not be the best way – to assess the therapeutic value of a "crude" plant with numerous constituents and myriad effects.

Cannabis contains several hundred compounds, including various flavonoids and polyphenols, aromatic terpenes, and dozens of minor cannabinoids, in addition to CBD and THC. Many of these compounds have

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<sup>11</sup> Pamplona, Fabricio A., et al. "Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-Analysis." *Frontiers in Neurology*, vol. 9, 12 Sept. 2018, doi:10.3389/fneur.2018.00759.

<sup>12</sup> Boehnke, Kevin F., et al. "Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain." *The Journal of Pain*, vol. 17, no. 6, June 2016, pp. 739–744., doi:10.1016/j.jpain.2016.03.002.

<sup>13</sup> Venderová, K., Růžička, E., Voříšek, V. and Višňovský, P. (2004), Survey on cannabis use in Parkinson's disease: Subjective improvement of motor symptoms. *Mov. Disord.*, 19: 1102-1106. doi:10.1002/mds.20111

<sup>14</sup> "Understanding CBD Report." *Understanding CBD Report*, Hello MD and Brightfield Group, July 2017, www.brightfieldgroup.com/library/understanding-cbd-report.

<sup>15</sup> Boehnke, Kevin F., et al. "Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users With Chronic Pain." *The Journal of Pain*, vol. 20, no. 7, July 2019, pp. 830–841., doi:10.1016/j.jpain.2019.01.010.

specific healing attributes, but when combined they create what scientists refer to as a holistic “entourage effect” or “ensemble effect,” so that the therapeutic impact of the whole plant exceeds the sum of its single-molecule parts.<sup>16</sup> Scientists may not fully understand the biochemical nuances and intricacies of the entourage effect, but we are well past the point of questioning its existence and significance.

## CATEGORY A - HEALTH AND SAFETY RISKS

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Cannabis is still tainted by the stigma of reefer madness, the racially-charged, anti-marihuana propaganda campaign that portrayed cannabis as a mortal threat to vulnerable women and children. How ironic that the erstwhile “Assassin of Youth” should become the savior for children with catastrophic seizure disorders and other life-threatening conditions. In June 2018, the FDA approved Epidiolex, a CBD oil extract from cannabis, as a treatment for two refractory pediatric seizure disorders.

“Protecting the children,” including the fetus, continues to be a key PR theme of the federal government’s war on drugs. Concerns surrounding cannabis in pregnancy, however, have far outpaced scientific data showing ill effects.

### QUESTION 2 – PREGNANT WOMEN

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- In human research, when confounding variables like alcohol and tobacco use are accounted for, reviews fail to find evidence that CBD or cannabis alone cause harm to the fetus, as Project CBD documented in a recent [report](#) to California’s Office of Environmental Health Hazard Assessment (See Appendix B).<sup>17</sup> Among the key findings:
  - There is insufficient evidence to conclude that maternal cannabis use causes low birth weight or long-term adverse developmental outcomes.<sup>18</sup>
  - Labeling cannabis, cannabis extracts, cannabis smoke, CBD or THC as reproductive toxins is not justifiable from high-quality scientific evidence and would misdirect public health and harm reduction efforts away from known teratogens, like alcohol and tobacco.
  - Although cannabinoids are not intrinsically toxic, they may amplify the toxic effects of alcohol, nicotine, and other teratogens. Thus, public health messages should be tailored towards pregnant women using multiple substances.

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<sup>16</sup> Russo, Ethan B. “Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects.” *British journal of pharmacology*. vol. 163,7 (2011): 1344-64. doi:10.1111/j.1476-5381.2011.01238.x

<sup>17</sup> Devitt-Lee, Adrian. “Pregnancy Complications: Can Cannabis Harm Your Fetus?” *Project CBD*, 23 Apr. 2019, [www.projectcbd.org/politics/cannabis-and-pregnancy-safety](http://www.projectcbd.org/politics/cannabis-and-pregnancy-safety).

<sup>18</sup> Goler N, Conway A, Young-Wolff KC. Data Are Needed on the Potential Adverse Effects of Marijuana Use in Pregnancy. *Ann Intern Med*. [Epub ahead of print 21 August 2018]169:492–493. doi: 10.7326/M18-1141

## QUESTION 1 – LIVER TOXICITY

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- Bogus science and inept reporting have promulgated misinformation about CBD and liver toxicity. Although there are real risks involved in some patient populations consuming large quantities of CBD, that risk is minimal for the vast majority of CBD consumers. In the real world, CBD consumers are not ingesting 0.25% of their body weight, the dose of CBD administered to mice in a flawed 2019 [study](#) purporting to demonstrate that CBD causes liver damage. In that study, scientists force-fed mice up 2460 mg/kg of CBD. These ridiculously large dosages were 100 times higher than the amount of CBD administered to epileptic children in clinical trials of Epidiolex. Project CBD has published an in-depth [critique](#) of preclinical research that correlates liver damage in humans to that observed in mice when they are administered massive doses (See Appendix C).<sup>19</sup> This type of research undermines serious efforts to understand the real risks of CBD and the problems it might actually cause.
- When consumed in large amounts, CBD can inhibit drug-metabolizing enzymes. The Epidiolex data showed that around 25-50 mg/kg/day of CBD isolate sometimes caused issues with the liver, but there are important caveats. Of particular concern is the reported elevation in the liver enzymes ALT and AST. This occurs in roughly 5-15% of children in Epidiolex trials. However, nearly every report involves the concurrent use of valproate, a powerful anti-epileptic drug that can cause problems in and of itself.<sup>20</sup> The resulting elevation in the levels of these liver enzymes could be understood as the result of a severe drug-drug interaction. Regardless, many neurologists maintain that the combination of CBD and valproate can be an effective epilepsy treatment.<sup>21,22</sup> Thus, doctors find it can be helpful to add CBD to a treatment regime that includes valproate, with the understanding that a patients' liver function will need to be monitored. The co-administration of CBD and clobazam, which also has a high likelihood of drug interactions, is another combination that pediatric neurologists find works well – at least anecdotally.
- The elevation of liver enzymes is indicative of stress on the liver, which could cause damage if it continues unabated. This can be safely managed when monitored by a doctor willing to adjust medications as needed. Additionally, these issues resolve when people stop taking CBD or reduce their dose. Thus far, there have been no reports of lasting harm when CBD treatment was ceased.

## QUESTION 3 – DRUG INTERACTIONS

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<sup>19</sup> Devitt-Lee, Adrian. "Is CBD Toxic to the Liver?" *Project CBD*, 11 July 2019, [www.projectcbd.org/science/cbd-toxic-liver](http://www.projectcbd.org/science/cbd-toxic-liver).

<sup>20</sup> Ghodke-Puranik, Yogita et al. "Valproic acid pathway: pharmacokinetics and pharmacodynamics." *Pharmacogenetics and genomics* vol. 23,4 (2013): 236-41. doi:10.1097/FPC.0b013e32835ea0b2

<sup>21</sup> Szaflarski, Jerzy P. et al. "Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study." *Epilepsy & Behavior*, Volume 87, Oct 2018, 131 - 136

<sup>22</sup> Sekar, Krithiga, and Alison Pack. "Epidiolex as adjunct therapy for treatment of refractory epilepsy: a comprehensive review with a focus on adverse effects." *F1000Research* vol. 8 F1000 Faculty Rev-234. 28 Feb. 2019, doi:10.12688/f1000research.16515.1

- CBD and THC can alter the metabolism of many commonly consumed pharmaceuticals. Project CBD has published an extensive [report](#) on cannabinoid-drug interactions to help health professionals and patients anticipate and avoid problematic outcomes, but also to take advantage of situations where cannabis and pharmaceuticals can act synergistically in a positive way (See Appendix D).<sup>23</sup> Key findings:
  - Based on observations regarding the widespread use of raw cannabis flower and full-spectrum cannabis oil, it does not appear that there have been many contraindications due to interactions with other drugs. The clinical use of Sativex (a 1:1 CBD:THC sublingual tincture) and Marinol (a pure, synthetic THC pill) have resulted in few, if any, reported adverse events attributable specifically to interactions with pharmaceuticals.
  - To the extent that there have been problematic drug interactions with cannabinoids, these have involved high doses of nearly pure CBD isolates, not cannabis in general. Even though THC is an intoxicant and CBD is not, the fact that people tend to use much higher doses of pure CBD makes it a much riskier player in metabolic drug interactions.
  - CBD is intrinsically safe, but when extracted from the plant and concentrated as an isolate, high doses are necessary for therapeutic efficacy. Whole plant CBD-rich extracts have a broader therapeutic window and are effective at lower doses than single-molecule CBD. Problems can arise when a patient combines a high dose of an otherwise benign CBD isolate with a pharmaceutical that has a very narrow window between its therapeutic and toxic levels. The FDA might consider requiring a warning label for high-dose CBD isolate products.
  - Ten milligrams of THC in a cannabis product is a generous dose for a naïve patient and sufficiently psychoactive for the occasional recreational user. (THC has its own built-in dysphoric guard rails – consume too much and you’ll know you’ve hit your limit.) Ten mgs of THC combined with an equal amount of CBD in a Sativex tincture hit the analgesic sweet spot in clinical trials. These are moderate doses compared to the amount of single molecule CBD (Epidiolex) administered to epileptic children in clinical trials – up to 50 mg per kilogram. CBD doses as high as 2000 mg are not uncommon among patients who obtain CBD isolates from internet storefronts and other unregulated sources.

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<sup>23</sup> Devitt-Lee, Adrian. “A Primer on Cannabinoid-Drug Interactions.” *Project CBD*, 25 Sept. 2018, [www.projectcbd.org/sites/projectcbd/files/downloads/cannabinoid-drug-interactions\\_2018-10-11.pdf](http://www.projectcbd.org/sites/projectcbd/files/downloads/cannabinoid-drug-interactions_2018-10-11.pdf).

- Limited preclinical research indicates that administering CBD and/or THC in conjunction with first-line chemotherapy drugs could potentiate the latter.<sup>24,25,26</sup> The clinical translation would imply a reduction in the dosage of highly toxic chemo necessary to treat the cancer. This is an example of a potentially beneficial cannabinoid-drug interaction. If this translates to human experience, it would be a huge benefit. But if pure CBD delays chemo metabolism, dangerously high levels of a toxic drug could accumulate unless the dose of chemotherapy is reduced and properly managed. The fact that cannabinoids make radiation and chemotherapy both more tolerable and seemingly more effective is an area worth studying.

## QUESTION 1 – ADDICTION

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The abuse potential of cannabis is limited - along the lines of overeating or caffeine addiction - and the symptoms of withdrawal in people with chronic cannabis use disorder are mild compared to more dangerous drugs of abuse (opioids, amphetamines, alcohol). CBD actually shows anti-addictive properties in animal model experiments.<sup>27,28</sup> Given the magnitude of the current opioid crisis, medical cannabis should be investigated as a harm reduction treatment for opioid addiction, as Project CBD urged in a special [report](#) on cannabis and opioids (See Appendix E).<sup>29</sup> Here are some key findings:

- Randomized controlled trials have shown that CBD-rich and THC-rich cannabis oil can be an effective treatment for chronic neuropathic pain and can improve the pain relief that opioids provide. Administering opioids and cannabis together results in a greater-than-addictive analgesic effect, a synergistic reduction of pain. Chronic pain patients who use medical cannabis report they experience a decrease in opioid use, a decreased number of medications and side effects, and an improved quality of life.
- Supplementing an opioid-based pain-management regimen with cannabis could result in lower doses of opioids required for adequate analgesia. Lower doses of opioids will reduce the number of overdose deaths. This is an example of a potentially beneficial cannabinoid-drug interaction. Cannabis can prevent opioid tolerance building and the need for dose escalation. Cannabis can also decrease the symptoms of opioid withdrawal — nausea, vomiting, spasms, cramping, insomnia.

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<sup>24</sup> Sandra Blasco-Benito, et al. "Appraising the "entourage effect": Antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer," *Biochemical Pharmacology*, Vol 157(2018) p 285-293, <https://doi.org/10.1016/j.bcp.2018.06.025>.

<sup>25</sup> Torres, Sofia, et al. "A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma." *Mol Cancer Ther* January 1 2011 (10) (1) 90-103; DOI: 10.1158/1535-7163.MCT-10-0688

<sup>26</sup> McAllister, S.D., Soroceanu, L. & Desprez, PY. *J Neuroimmune Pharmacol* (2015) 10: 255.

<https://doi.org/10.1007/s11481-015-9608-y>

<sup>27</sup> Prud'homme, Mélissa et al. "Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence." *Substance abuse: research and treatment* vol. 9 33-8. 21 May. 2015, doi:10.4137/SART.S25081

<sup>28</sup> Gonzalez-Cuevas, Gustavo et al. "Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle." *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* vol. 43,10 (2018): 2036-2045. doi:10.1038/s41386-018-0050-8

<sup>29</sup> Sulak, Dustin. "America's Opiate Addiction Crisis and How Medical Cannabis Can Help." *Project CBD*, Aug. 2016, [www.projectcbd.org/sites/projectcbd/files/downloads/handout\\_sulak\\_1.pdf](http://www.projectcbd.org/sites/projectcbd/files/downloads/handout_sulak_1.pdf).

- Preclinical [research](#) suggests that CBD is protective against neurodegeneration caused by binge-drinking and may have therapeutic properties for alcohol, tobacco, opioid, cocaine, and psychostimulant addiction.<sup>30</sup> There's also evidence that CBD can [aid](#) in addiction recovery by preventing relapse due to its effects on cue-induced memory.<sup>31</sup>

## QUESTION 2 – MENTAL ILLNESS

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- The claim that cannabis causes or precipitates psychosis has long been invoked as a reason for prohibiting cannabis. With hundreds of millions of dollars invested and over a century of dedicated research, the psychosis argument remains weak. Epidemiological research indicates there is little correlation between rates of cannabis use and schizophrenia in Western societies. But there is consistently an association between cannabis use and the development of psychosis. This could mean that cannabis might precipitate schizophrenia in vulnerable populations. Or it could mean that people use cannabis to self-medicate, even before a diagnosis of schizophrenia. Some research suggests that schizophrenia predicts cannabis use, rather than the other way around.<sup>32</sup>

## QUESTION 4 – RESPONSIBLE USE

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- Learning how to optimize one's therapeutic use of CBD and cannabis may involve some trial and error. CBD can be effective at a wide range of dosages: lower doses are sometimes more effective therapeutically than higher doses. Project CBD has published a detailed [guide](#) on cannabis dosing based on data aggregated from physicians, patients, and medical scientists who are exploring the therapeutic attributes of CBD and other cannabis components (See Appendix F).<sup>33</sup>
- Cannabis prohibition is a fragile edifice built on a mountain of falsehoods. The most egregious falsehood of all is that herbal cannabis with more than 0.3 percent THC is a dangerous substance with no medical value. Lost amidst the steady drumbeat of hyperbolic anti-cannabis confabulations over the years is an awareness of some of the real but subtle risks associated with chronic cannabis consumption – such as dehydration, drug interactions, and dysphoria. Cannabis, a hypotensive herb, might not be the best medicine for someone with low blood pressure. And dehydration could be an issue for any astringent botanical that is consumed on a regular basis. Contraindications and drug interactions are easily manageable. If THC-rich products induce dysphoria, one can try non-intoxicating CBD-rich options.

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<sup>30</sup> Hamelink, Carol et al. "Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity." *The Journal of pharmacology and experimental therapeutics* vol. 314,2 (2005): 780-8.

doi:10.1124/jpet.105.085779

<sup>31</sup> Devitt-Lee, Adrian. "Drug Memories: CBD & Addiction." *Project CBD*, 13 Apr. 2018, [www.projectcbd.org/medicine/drug-memories-cbd-addiction](http://www.projectcbd.org/medicine/drug-memories-cbd-addiction).

<sup>32</sup> Gage, S H et al. "Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study." *Psychological medicine* vol. 47,5 (2017): 971-980.

doi:10.1017/S0033291716003172

<sup>33</sup> Lee, Martin A. "CBD & Cannabis Dosage Guide." *Project CBD*, 1 Apr. 2019, [www.projectcbd.org/how-to/cbd-dosage](http://www.projectcbd.org/how-to/cbd-dosage).

## CATEGORY B – MANUFACTURING AND PRODUCT QUALITY

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Manufacturing cannabis products starts with the plant. The plant is the alpha and omega of cannabis oil extraction and production. There are [several ways](#) to extract oil from cannabis (utilizing solvents such as super-critical CO<sub>2</sub>, ethanol, or hydrocarbons) (See Appendix G). Each method has its pros and cons. Some are safer and more effective than others. It's not rocket science. Other industries successfully employ the same extraction technologies in accordance with already established safe manufacturing standards. [Reference / link to AHPA].

The purpose of extracting oil from cannabis is to make CBD and other components of the plant available in a highly concentrated form. After it is extracted from the plant matter and the solvent is removed, the CBD-rich (or THC-rich) oil may be refined and formulated into a variety of consumable products – edibles, tinctures, soft gels, vape oil cartridges, beverages, topicals, and more.

But many CBD products are manufactured without regulatory oversight and the quality of these products can vary greatly, depending on several factors, most notably: the health of the soil in which cannabis is grown; the presence of pesticide and solvent residues in the oil extract; and the problematic use of toxic thinning agents and flavor additives that may have adverse health effects.

## QUESTION 2 – BIOACCUMULATION AND HEAVY METAL CONTAMINATION

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Cannabis is a remarkably proficient “bio-accumulator” — meaning the plant naturally sucks up toxins from the soil.<sup>34</sup> That's wonderful for restoring a poisoned landscape, but it's not so great for making ingestible and inhalable medicinal oil products. Oil extracted from cannabis will concentrate heavy metals and other toxins drawn from the soil in which it's grown, along with the CBD and other desirable plant components.<sup>35</sup> The phyto-remedial properties of cannabis underscore the importance of cultivating resin-rich plants in a clean environment.

CBD oil is extracted from the resinous trichomes of cannabis plants. The amount of CBD and THC present in the trichomes will depend on the particular variety of cannabis or hemp. Low-resin industrial hemp (legally defined as cannabis with less than 0.3 percent THC by dry weight) has fewer trichomes – and therefore less oil – than high-resin cannabis varieties (marijuana). Therefore, a large amount of hemp biomass is required to extract a relatively small amount of CBD oil – which increases the risk of contaminants.

Compared to high-resin cannabis, low-resin industrial hemp is more vulnerable to pest and mold infestation because the resin contains terpenes as well as cannabinoids that repel predators, attract beneficial insects, and protect plants from blight. With increased risk of pests comes an increased risk of pesticide and fungicide applications, which can be concentrated into toxic levels when cannabinoid oils are extracted from the flower.

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<sup>34</sup> Girdhar, Madhuri et al. “Comparative assessment for hyperaccumulatory and phytoremediation capability of three wild weeds.” *3 Biotech* vol. 4,6 (2014): 579-589. doi:10.1007/s13205-014-0194-0

<sup>35</sup> McPartland J.M., McKernan K.J. (2017) Contaminants of Concern in Cannabis: Microbes, Heavy Metals and Pesticides. In: Chandra S., Lata H., ElSohly M. (eds) *Cannabis sativa L. - Botany and Biotechnology*. Springer, Cham

## QUESTION 2 – PESTICIDES, FUNGICIDES, AND SOLVENT RESIDUES

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There are many ways to administer cannabis products, and this poses unique challenges to regulators who are tasked with setting allowable limits for heavy metals, pesticides, and solvent residues. Problems have arisen in part because regulators don't always take into account how CBD and various cannabis products are actually consumed. Different modes of administration (ingesting, smoking and vaping) may warrant different allowable action limits to protect cannabis and CBD consumers from toxic exposure, as Project CBD indicated in a [report](#) to California's Bureau of Cannabis Control (See Appendix H). This report presented a detailed critique of California's testing requirements for cannabis products and emphasized the following:

- Federal and state agencies have compiled safety data pertaining to the oral ingestion of pesticides and solvent residues, but there is little safety data regarding smoked or vaporized pesticides and solvents. That's because the tobacco industry lobbied to ensure that scientific data on health and safety was not used to inform laws or regulations. Tobacco's poor regulatory standards with respect to pesticides should not serve as a model for the emerging cannabis industry.
  - Relatively little is known about the health effects of heating or burning pesticides. Some pesticides will become safer when burned, while many others will break down into much more toxic compounds. Pesticides degrade into stronger toxins at temperatures that cause cannabinoids to vaporize. The widely used pesticide myclobutanil, sold as Eagle-20, decomposes into hydrogen cyanide when heated.
  - Regulations need to be based on sound scientific data. If safety data on burning and inhaling pesticides is not yet available, then there should be provisions for updating and adjusting allowable limits as more toxicological data becomes available.
- Solvents are classified into one of three groups by the FDA. Given that cannabis oil can be safely extracted with Class 3 solvents like ethanol and butane, we recommend banning the use of all highly toxic Class 1 solvents, including benzene, as unsafe and unnecessary. Project CBD further recommends that regulators work with cannabis product-makers to determine if Class 2 solvents, such as chloroform, and dichloromethane, are necessary for extracting CBD and other cannabinoids. If safer options are viable, Class 2 solvents should also be banned for use in manufacturing cannabis extracts.
- There should be a zero tolerance policy for spraying cannabis with neonicotinoids (e.g., acetamiprid, imidacloprid), pesticides which are a factor in the worldwide decline of bee populations.
- Mold is one of the most common contaminants found on cannabis. It is essential that products made from low-resin hemp or high-resin cannabis be tested for mold. California's regulations for mold on cannabis products are far too lax, as Project CBD noted in its [critique](#) of California's revised regulatory requirements (See Appendix I).

Well-regulated testing requirements are essential for the legal cannabis industry and the consumers that it serves. Labs should be certified by groups such as the International Organization for Standardization or the International Electrotechnical Commission to ensure the accuracy and consistency of analytical data, which has been problematic in the past.

## QUESTION 2 – TOXIC THINNING AGENTS AND FLAVOR ADDITIVES IN VAPE OIL CARTRIDGES

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Many CBD consumers assume that vaping cannabis or hemp oil is a healthier method of administration than inhaling smoke, which contains noxious substances that can irritate the lungs. Theoretically a vaporizer heats the cannabis oil concentrate without burning it so the active ingredients are inhaled but no smoke is involved.<sup>36</sup> But there may be a serious downside to vaping CBD oil and other cannabis oil extracts. Vape pens contain a battery-operated heating mechanism, which at high temperatures can transform solvents, thinning agents and flavor additives into carcinogens and other dangerous toxins. Project CBD has been [sounding the alarm](#) about potential harms from vaping poor quality, hemp-derived CBD oil since 2015, a year before e-cigarettes came under the FDA's regulatory control (See Appendix J). Here are some of our concerns:

- Many vape oil cartridges include propylene glycol (PG) or polyethylene glycol (PEG) as a thinning agent, but neither has been safety tested by the FDA for inhalation when heated. Because of low oral toxicity, PG is classified by the FDA as "generally recognized as safe" for ingestion as a food additive. PG is also the primary ingredient in a majority of nicotine-infused e-cigarette solutions. At high temperatures, PG and other vaping additives convert into carbonyls, a group of cancer-causing chemicals that includes formaldehyde, a toxin linked to spontaneous abortions and low birth weight.
- To date there is no conclusive evidence that frequent users will develop cancer or other illnesses if they inhale the contents of vape oil cartridges. That's because little is actually known about the short-term or long-term health effects of inhaling PG and other ingredients that are present in flavored vape pen cartridges. Many of these prefilled cartridges are poorly labeled with little or no meaningful information on their contents. The possibility that vape pens might expose people to unknown health hazards underscores the importance of adequate safety testing for these products, which thus far has been lacking.
- FDA-approved flavoring agents are prevalent in nicotine e-cig products and CBD/cannabis vape oil cartridges, but these additives were officially approved on the basis of safety tests for ingestion and topical application, not for inhalation as heated compounds. A 2018 [study](#) by University of

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<sup>36</sup> It's worth noting that "vaporizing" can refer to two separate forms of administration. There are dry-herb vaporizers, which gently heat whole plant flower to temperatures below combustion to create a true vapor. These vaporizers may very well provide a safer form of inhalation than smoking. There are also vape pens, similar to e-cigarettes, which involve heating a cartridge filled with cannabis/CBD oil to very high temperatures (some have been recorded to achieve temperatures of 1000F) and inhaling the resulting smoke or vapor. These likely have a less safe profile, and likely have similar risks to smoking.

Rochester scientists found that exposure to commonly used e-cigarette flavoring chemicals and liquids is toxic to white blood cells.<sup>37</sup>

- Many flavoring compounds are toxic when heated and inhaled; cinnamon, vanilla and cream flavors among the most toxic. A recent [report](#) by Yale University researchers showed that mixing chemical flavoring agents is more dangerous than exposure to a single additive.<sup>38</sup> Moreover, some flavor additives interact with PG and PEG to form noxious acetal compounds. When heated and inhaled these inflammatory chemicals persist in the body for some time and irritate the lungs.
- A chemical called diacetyl is added to e-cigarettes and vape oil cartridges to simulate various buttery flavors, ranging from cream to vanilla and caramel. This particular compound is known to cause "popcorn lung," a crippling and sometimes fatal respiratory illness. A shocking 2015 [study](#) of flavored e-cigarettes found that 39 out of 51 tested brands contained diacetyl.<sup>39</sup> It should be banned from use in vape oil.

The precautionary principle mandates that any thinning agent or flavor-enhancing chemical that has not been safety tested for heat and inhalation exposure should be prohibited as a cannabis oil additive.

#### QUESTION 4 – GLOSSARIES

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See Appendices K and L for common product definitions and terminology used in the cannabis industry.

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<sup>37</sup> Muthumalage, Thivanka, et al. "Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine." *Frontiers in Physiology*, 11 Jan. 2018, [www.frontiersin.org/articles/10.3389/fphys.2017.01130/full](http://www.frontiersin.org/articles/10.3389/fphys.2017.01130/full).

<sup>38</sup> Eythropel, Hanno C, et al. "Formation of Flavorant–Propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids." *Oxford Academic*, Oxford University Press, 18 Oct. 2018, [academic.oup.com/ntr/advance-article/doi/10.1093/ntr/nty192/5134068](http://academic.oup.com/ntr/advance-article/doi/10.1093/ntr/nty192/5134068).

<sup>39</sup> Allen, Joseph G, et al. "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes." *National Institute of Environmental Health Sciences*, Environmental Health Perspectives, 1 June 2016, [ehp.niehs.nih.gov/doi/10.1289/ehp.1510185](http://ehp.niehs.nih.gov/doi/10.1289/ehp.1510185).

## CATEGORY C – MARKETING/LABELING/SALES

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Consumers need to know what they're consuming. One of the fundamental functions of the FDA is to ensure just that. It's no different for cannabis and CBD products – consumers need to know how much and the source of the CBD they are consuming. Thus far, however, there has been little federal oversight for manufacturing CBD products, and this has fostered confusion and deception.

The Journal of the American Medical Association and other sources have reported that many unregulated, hemp-derived CBD oil products are mislabeled as to CBD and THC content.<sup>40,41,42,43</sup> Some hemp-derived CBD brands have falsely claimed full-spectrum CBD-rich oil is in their products, but lab tests of several samples revealed only one cannabinoid – CBD – was present, indicating that these products were made with a CBD isolate rather than a more efficacious whole plant CBD-rich extract.<sup>44</sup> There are other mislabeling issues, as well, that warrant careful scrutiny, including (but not limited to) exaggerated or unsubstantiated medical claims that CBD businesses make about their products.

### QUESTION 4 – SUGGESTIONS

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Most labeling problems are easily correctable and preventable with requisite lab testing and sensible regulations. Labels that accurately reflect the content of CBD products are essential for consumers who seek to make informed decisions about using CBD as a health aide. Accordingly, Project CBD suggests the following:

- Regulations should require specific information on CBD product labels, including the amount of CBD and THC per serving, not just the total cannabinoid content for the entire product.
- Labels should indicate whether the product contains a CBD isolate, a full-spectrum CBD-rich oil extract, or a so-called broad-spectrum extract without THC.
- Given the possibility of drug interactions when a large dose of CBD is consumed by people taking pharmaceuticals, the FDA should require a warning label for products consisting of high-dose CBD isolates (See Appendix C).
- Poorly processed CBD oil may be contaminated with toxic solvent and pesticide residues, thinning agents, corn syrup, artificial flavors and colors, and other toxins. Product labels must indicate any additive ingredients that are present in CBD oil products.

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<sup>40</sup> Bonn-Miller, Marcel O et al. "Labeling Accuracy of Cannabidiol Extracts Sold Online." *JAMA* vol. 318,17 (2017): 1708-1709. doi:10.1001/jama.2017.11909

<sup>41</sup> Freedman, D.A. and Patel, A.D., 2018. Inadequate Regulation Contributes to Mislabeled Online Cannabidiol Products. *Pediatric Neurology Briefs*, 32, p.3. DOI: <http://doi.org/10.15844/pedneurbriefs-32-3>

<sup>42</sup> Jikomes, Nick, and Michael Zoorob. "The Cannabinoid Content of Legal Cannabis in Washington State Varies Systematically Across Testing Facilities and Popular Consumer Products." *Scientific Reports*, vol. 8, no. 1, 2018, doi:10.1038/s41598-018-22755-2.

<sup>43</sup> Justin L. Poklis, Haley A. Mulder, Michelle R. Peace, The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids, *Forensic Science International*, Volume 294, 2019, Pages e25-e27, ISSN 0379-0738, <https://doi.org/10.1016/j.forsciint.2018.10.019>.

<sup>44</sup> "CBD & Hemp Extract Supplements Review." *ConsumerLab.com*, 8 Feb. 2019, [www.consumerlab.com/reviews/cbd-oil-hemp-review/cbd-oil/PREVIEW/](http://www.consumerlab.com/reviews/cbd-oil-hemp-review/cbd-oil/PREVIEW/).

Some CBD hemp companies make false claims that the CBD in their products is extracted from hemp seeds and/or hemp stalk. The stalk of the hemp plant is not a viable source of CBD oil, which is concentrated on the flower tops and to a lesser extent on the leaves of cannabis. While hemp seeds are an excellent source of protein-rich omega 3 fatty acids, the seeds themselves don't contain CBD, THC or any other cannabinoids. CBD oil is not the same as "hemp oil" or "hempseed oil," and this should be clearly indicated on product labels to avoid confusion.

#### QUESTION 4 – HONOR THE WHOLE PLANT

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When the endocannabinoid system doesn't function properly, our health suffers. Scientific studies have shown that the endocannabinoid system is dysregulated in nearly all pathological conditions. According to Pal Pacher and Geroge Kunos, leading scientists with the National Institutes of Health, "[M]odulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans, including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy induced nausea and vomiting among many others."<sup>45</sup>

By modulating the endocannabinoid system and improving endocannabinoid tone, CBD-rich and THC-rich cannabis can slow, or in some cases stop, the progression of various diseases.<sup>46</sup> The federal government, however, refuses to acknowledge what people have known for thousands of years – that cannabis is a medically useful plant.

Medical scientists know a great deal about how cannabis components confer various effects through multiple molecular pathways. The therapeutic use of cannabis for millennia is a testament to its safety and efficacy. Ensuring the safety and quality of CBD-rich and cannabinoid-based products, while creating an avenue to study the medical impacts of this versatile plant, should be the FDA's utmost priority in crafting regulation.

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<sup>45</sup> Pacher, Pál, and George Kunos. "Modulating the endocannabinoid system in human health and disease--successes and failures." *The FEBS journal* vol. 280,9 (2013): 1918-43. doi:10.1111/febs.12260

<sup>46</sup> Russo, Ethan B. "Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes." *Cannabis and Cannabinoid Research*, vol. 1, no. 1, 2016, pp. 154–165., doi:10.1089/can.2016.0009.

## REGULATING CANNABIS AS A TRADITIONAL HERBAL MEDICINE

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Many countries around the world have robust systems that govern traditional and herbal medicines, as well as pharmaceutical drugs.<sup>47</sup> The United States, however, does not have a specific entity governing plant medicines, which fall under the weak regulatory purview of the Dietary Supplement Health and Education Act (DSHEA) of 1994.

This Congressional legislation has facilitated significant advances in expanding the supplement industry and carving out a unique category of products between "food" and "drug." But the DSHEA has failed to implement an adequate regulatory mechanism to ensure the quality and safety of herbal supplements in the United States.<sup>48,49,50,51,52,53</sup>

Manufacturers are supposed to submit documentation to the FDA showing that new supplements are safe and accurately labeled. However, if the FDA does not review the materials within a 75-day review period, the products are allowed to market regardless - without confirmation of regulatory compliance. The DSHEA does not require that these products be tested for safety or purity until *after* serious injury or death have been reported.

Responding with alacrity to reports of adverse events hasn't been a strong suit of the DSHEA system. The lack of rigorous regulatory oversight has resulted in several dangerous supplements being widely marketed for years after reports of serious consequences were initially noted by the FDA. It took nearly ten years, over 150 deaths, and a court battle to remove Ephedra, a popular performance enhancer in the '90s and '00s, from the marketplace.<sup>54</sup>

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<sup>47</sup> World Health Organization. (2005). *National policy on traditional medicine and regulation of herbal medicines*. Retrieved from World Health Organization website: <https://apps.who.int/medicinedocs/en/d/Js7916e/>

<sup>48</sup> Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. "Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings." *JAMA Netw Open*. Published online October 12, 2018;1(6):e183337. doi:10.1001/jamanetworkopen.2018.3337

<sup>49</sup> Chen Y, et al. "Determination of Multiresidue Pesticides in Botanical Dietary Supplements Using Gas Chromatography–Triple-Quadrupole Mass Spectrometry (GC-MS/MS)." *Journal of Agricultural and Food Chemistry*. 2016 64 (31), 6125-6132 DOI: 10.1021/acs.jafc.6b00746

<sup>50</sup> Mathews, Neilson M. "Prohibited Contaminants in Dietary Supplements." *Sports health* vol. 10,1 (2018): 19-30. doi:10.1177/1941738117727736

<sup>51</sup> O'connor, Anahad. "What's in Those Supplements?" *The New York Times*, The New York Times, 3 Feb. 2015, [well.blogs.nytimes.com/2015/02/03/sidebar-whats-in-those-supplements/](http://well.blogs.nytimes.com/2015/02/03/sidebar-whats-in-those-supplements/).

<sup>52</sup> Harris, Gardiner. "Study Finds Supplements Contain Contaminants." *The New York Times*, The New York Times, 26 May 2010, [www.nytimes.com/2010/05/26/health/policy/26herbal.html](http://www.nytimes.com/2010/05/26/health/policy/26herbal.html).

<sup>53</sup> Hamblin, James. "Why Vitamins and Other 'Dietary Supplements' Can Contain Anything." *The Atlantic*, Atlantic Media Company, 28 June 2016, [www.theatlantic.com/health/archive/2016/06/supplements-make-tobacco-look-easy/488798/](http://www.theatlantic.com/health/archive/2016/06/supplements-make-tobacco-look-easy/488798/).

<sup>54</sup> "Why the FDA banned ephedra." *Harvard Health Publishing*, Harvard Medical School, March 2004, <https://www.health.harvard.edu/staying-healthy/ephedra-ban>.

Consumer safety organizations contend that anywhere between 20-70% of supplements are mislabeled and do not contain what they say they do.<sup>55,56</sup> Moreover, there has been significant evidence of supplement contamination with pharmaceuticals, as well as pesticides. The National Institutes of Health has advised caution when it comes to consuming health supplements, warning that many have been tainted with contaminants.<sup>57</sup>

## UNDERFUNDED ENFORCEMENT

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A majority of consumers, including health professionals, make the errant assumption that supplements available on the market have been tested for safety and efficacy by the government and that any adverse effects are indicated on the label.<sup>58</sup> This is simply not the case. Lethal outcomes from supplements are very much the exception, not the rule.<sup>59</sup> But without adequate testing requirements there is little consumers can do to confirm that the products they buy are uncontaminated and properly labeled.

The federal government has consistently failed to establish procedures for ensuring that supplements going to market are safe and of high quality. A significant factor that undermines DSHEA enforcement efforts is inadequate funding. Only a tiny fraction of the \$920 million budget of the FDA's Center for Food Safety and Nutrition is allocated towards policing the \$31 billion supplement industry.<sup>60,61</sup>

Under the DSHEA, nearly 70% of manufacturers were in violation of the established Good Manufacturing Practices (GMPs) in 2013.<sup>62</sup> In order to ensure the safety of CBD and cannabis products, the adherence to established GMPs would need to be strictly enforced. Ethical operators manufacture safe and effective CBD products. But allowing producers to be responsible for their own quality control leads to poor manufacturing practices and fraud, as evidenced by data about pesticides, heavy metals, and other

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<sup>55</sup> Tucker J, Fischer T, Upjohn L, Mazzera D, Kumar M. Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. *JAMA Netw Open*. Published online October 12, 2018;1(6):e183337. doi:10.1001/jamanetworkopen.2018.3337

<sup>56</sup> Navarro, V. , Avula, B. , Khan, I. , Verma, M. , Seeff, L. , Serrano, J. , Stolz, A. , Fontana, R. and Ahmad, J. (2019), The Contents of Herbal and Dietary Supplements Implicated in Liver Injury in the United States Are Frequently Mislabeled. *Hepatology*, 3: 792-794. doi:[10.1002/hep4.1346](https://doi.org/10.1002/hep4.1346)

<sup>57</sup> "Using Dietary Supplements Wisely." *National Center for Complementary and Integrative Health*, U.S. Department of Health and Human Services, 15 Jan. 2019, [nccih.nih.gov/health/supplements/wiseuse.htm](https://nccih.nih.gov/health/supplements/wiseuse.htm).

<sup>58</sup> Dodge, T. ( 2016) Consumers' perceptions of the dietary supplement health and education act: implications and recommendations. *Drug Test. Analysis*, 8: 407– 409. doi: [10.1002/dta.1857](https://doi.org/10.1002/dta.1857).

<sup>59</sup> Although around 13% of supplements carry a third-party certification, those certifications do not guarantee safety, efficacy, or quality. [See <sup>59</sup> Cancio, Anthony & Eliason, Michael & Mercer, Jennifer & Tran, Thu & Deuster, Patricia & Stephens, Mark. (2012). Third-Party Certification of Dietary Supplements: Prevalence and Concerns. *Military medicine*. 177. 1460-3. 10.7205/MILMED-D-12-00069; and Donnamaria R. Jones, Korey B. Kasper, Patricia A. Deuster, Third-Party Evaluation: A Review of Dietary Supplements Dispensed by Military Treatment Facilities From 2007 to 2011, *MILITARY MEDICINE*, Volume 180, Issue 7, July 2015, Pages 737–741, <https://doi.org/10.7205/MILMED-D-14-00500>]

<sup>60</sup> Mathews, Neilson M. "Prohibited Contaminants in Dietary Supplements." *Sports health* vol. 10,1 (2018): 19-30. doi:10.1177/1941738117727736

<sup>61</sup> HHS Office of the Secretary, Office of Budget, and Ob. "FY 2018 Budget in Brief - FDA." *HHS.gov*, US Department of Health and Human Services, 23 May 2017, [www.hhs.gov/about/budget/fy2018/budget-in-brief/fda/index.html](http://www.hhs.gov/about/budget/fy2018/budget-in-brief/fda/index.html).

<sup>62</sup> Long J. "FDA GMP inspectors cite 70% of dietary supplement firms." *Natural Products Insider*. 2013.

contaminants found in CBD products throughout the unregulated market. A more rigorous, proactive approach to supplement regulation is advisable.<sup>63</sup>

Mislabeled products, pesticides, and contaminants -- these problems plague the fledgling CBD industry. Data presented at the FDA hearing on May 31, 2019, showed that many CBD products available online contained significantly different levels of CBD than those listed on the label, as well as potentially harmful unlisted compounds.

It's hard to see how this would improve if CBD and other cannabis products were regulated as supplements under the auspices of the DSHEA. Some have argued in favor of this approach.<sup>64</sup> But it doesn't appear that the existing regulatory system for supplements provides a robust enough framework to ensure that only safe, high-quality cannabis products get to market.

## NOT JUST A DRUG

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The foundational documents of the FDA clearly indicate that a drug “is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.” Additionally, a drug is defined as “an article (other than food) intended to affect the structure or any function of the body of man or other animals.”

By this definition, many people in the United States utilize herbal supplements in general and CBD products in particular in ways that would qualify their use as drugs. Currently, about 20% of the U.S. population takes herbal supplements, mostly to treat or manage an illness.<sup>65</sup> But herbal products aren't regulated as drugs. Instead they are regulated as supplements under the larger umbrella of “food.”

The FDA isn't generally in the business of approving plants as medicine, even though numerous pharmaceuticals are based on compounds found in medicinal herbs throughout the world.<sup>66</sup> While many of these drugs are available only through a physician's prescription, the whole plant varieties from which drugs are derived often remain available as herbal supplements. In 2015, for example, a Chinese pharmacist was awarded the Nobel Prize for her contribution to the discovery of the antimalarial drug artemisinin, an extract refined from wormwood. Her research was based on analyzing ancient medical texts, wherein the use of wormwood to treat malaria was referenced repeatedly.<sup>67</sup> Wormwood is still a widely used therapeutic herb.

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<sup>63</sup>See Nowak RE. “DSHEA's failure: why a proactive approach to dietary supplement regulation is needed to effectively protect consumers.” *Univ Ill Law Rev.* 2010;2010:1045–1068. [[Google Scholar](#)]

<sup>64</sup> United States. FDA. *Hearing Under 21 CFR Part 15: Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing.* May 31, 2019.

<sup>65</sup> Bent, Stephen. “Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center.” *Journal of general internal medicine* vol. 23,6 (2008): 854-9. doi:10.1007/s11606-008-0632-y

<sup>66</sup> Fabricant, Daniel S., and Norman R. Farnsworth. “The Value of Plants Used in Traditional Medicine for Drug Discovery.” *Environmental Health Perspectives*, vol. 109, 2001, p. 69., doi:10.2307/3434847.

<sup>67</sup> Jütte, R., et al. “Herbal medicinal products – Evidence and tradition from a historical perspective.” *Journal of Ethnopharmacology.* 2017.

There is precedent for approving a “[botanical drug](#)” within the FDA, though only two products have been accorded this status by the powers-that-be. Both contain highly purified and standardized extracts from botanical sources. Isolated extracts of CBD and THC from cannabis have already been approved as pharmaceuticals and, therefore, according to FDA policy, the botanical drug designation cannot apply to these single-molecule compounds.

Up until this point, the FDA has regulated CBD and THC just like any other pharmaceutical. But this might not be possible for much longer. We are now at a crossroads, and the FDA is faced with the unprecedented challenge of regulating hemp-derived CBD for general consumption as supplements, food additives, beverages, vape oil concentrates, artisanal extracts, tinctures, and raw herb. And not only CBD. Cannabis expresses incredibly complex biochemical diversity in which THC and CBD play major, but not all-encompassing, roles.<sup>68,69</sup>

Classifying CBD as a single-molecule drug is too narrow a designation. Nor should CBD products be relegated by default to the poorly regulated supplement sector with its grab-bag of vitamins, minerals, essential oils, plant-based tinctures, nutraceuticals, and replicates of endogenous neurotransmitters -- anything that's not pharma.

Even if federal officials were to make a sincere effort to strengthen DSHEA's enforcement capabilities, cannabis deserves recognition for its unique therapeutic attributes as an herbal adaptogen. Cannabis has a long and well-documented history as an herbal remedy in many countries, including the United States. The first evidence of its therapeutic use dates back nearly five thousand years to ancient China, and its continued use as a medicine over millennia is a testament to the plant's safety, efficacy, and enduring popularity.<sup>70,71,72</sup>

## OTHER REGULATORY MODELS

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How do other countries around the world regulate herbal products? What criteria are used to define a “traditional” herbal medicine and how does this vary in different cultures?<sup>73</sup> Could these examples help to

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<sup>68</sup> Russo, Ethan B. “Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects.” *British journal of pharmacology* vol. 163,7 (2011): 1344-64. doi:10.1111/j.1476-5381.2011.01238.x

<sup>69</sup> Ryan C. Lynch, Daniela Vergara, Silas Tittes, Kristin White, C. J. Schwartz, Matthew J. Gibbs, Travis C. Ruthenburg, Kymron deCesare, Donald P. Land & Nolan C. Kane (2016) Genomic and Chemical Diversity in *Cannabis*, *Critical Reviews in Plant Sciences*, 35:5-6, 349-363, DOI: [10.1080/07352689.2016.1265363](https://doi.org/10.1080/07352689.2016.1265363)

<sup>70</sup> Russo, E. (2007), History of Cannabis and Its Preparations in Saga, Science, and Sobriquet. *Chemistry & Biodiversity*, 4: 1614-1648. doi:[10.1002/cbdv.200790144](https://doi.org/10.1002/cbdv.200790144)

<sup>71</sup> Abel, Ernest L. *Marihuana: the First Twelve Thousand Years*. Springer Science+Business Media, 1980.

<sup>72</sup> “Early Medical use of Cannabis.” *Nature* 363.6426 (1993): 215. [ProQuest](https://www.proquest.com/life-physical-sciences/early-medical-use-of-cannabis/docview/215). 12 July 2019 .

<sup>73</sup> See Ibid. In order for an herbal medicinal product to be considered “traditional,” the European Union requires the product to have been in traditional use for 30 years, with use for at least 15 years within the EU. Australia requires “well documented [traditional use] over an extended period of time” or approximately 75 years. [Australian Government Department of Health Therapeutic Goods Administration. (2018). *Australian regulatory guidelines for complementary medicines*. Retrieved from Therapeutic Goods Administration website: <https://www.tga.gov.au/sites/default/files/australian-regulatory-guidelines-complementary-medicines-argcm-v8.0.pdf>] A rigorous review of traditional use, including any historically identified side effects, needs to be considered in any product potentially considered a traditional herbal product. [See Jütte, R., et al. “Herbal medicinal products – Evidence and tradition from a historical perspective.” *Journal of Ethnopharmacology*. 2017.]

inform U.S. regulatory policy that governs not only CBD, but whole plant cannabis and other herbal medicines, as well?

The World Health Organization has published extensively on the subject of regulating herbal medicines,<sup>74,75,76,77</sup> as has the American Herbal Products Association.<sup>78,79</sup>

The 2019 WHO report “[WHO Global Report on Traditional and Complementary Medicine](#)” outlines how 179 countries around the world regulate traditional and herbal medicines. Ninety-one have established national policies related to herbal medicines. Many countries (Indonesia, China, Australia, Korea, India, and Thailand, to name a few) have registered hundreds if not thousands of herbal medicines with an official regulatory agency.<sup>80</sup>

The European Union (EU) has established a Committee on Herbal Medicinal products and Food Supplements Directive with consumer protection in mind. But the process to place a product on the "positive list" -- the approved list of supplements that can be marketed in the EU -- is prohibitively expensive. It's estimated to cost €100,000-400,000 to conduct the tests necessary to be considered for inclusion on the list.<sup>81</sup> The high price point favors large processors and all but prohibits smaller companies from participation.

In Australia, herbal medicines are regulated as complementary medicines under the Therapeutic Goods Administration (TGA) in line with the Australian Regulatory Guidelines for Complementary Medicines. Herbal products are considered non-prescription medicines and are required to state their status as traditional medicines on the label. The fees associated with selling these products are significantly less than those in the EU.<sup>82</sup> Australia and the EU both require pre-market lab testing by a state lab. Recently, however, the quality of herbal products available in the Australian marketplace and the permitted list of health claims have been criticized by scientists and doctors. Proof of efficacy is not required by the TGA

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<sup>74</sup> “Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines.” *World Health Organization*, World Health Organization, 1993, [apps.who.int/medicinedocs/en/d/Jh2946e/#Jh2946e](https://apps.who.int/medicinedocs/en/d/Jh2946e/#Jh2946e).

<sup>75</sup> “Quality Control Methods for Herbal Materials.” *World Health Organization*, World Health Organization, 2011, [apps.who.int/medicinedocs/en/m/abstract/Jh1791e/](https://apps.who.int/medicinedocs/en/m/abstract/Jh1791e/).

<sup>76</sup> “WHO Guidelines for Assessing Quality of Herbal Medicines with Reference to Contaminants and Residues.” *World Health Organization*, World Health Organization, 2007, <http://apps.who.int/medicinedocs/documents/s14878e/s14878e.pdf>

<sup>77</sup> “WHO Guidelines on good manufacturing Practices (GMP) for Herbal Medicines.” *World Health Organization*, World Health Organization, 2007, <http://apps.who.int/medicinedocs/documents/s14215e/s14215e.pdf>

<sup>78</sup> “AHPA Issues Guidance on Good Agricultural and Collection Practices and Good Manufacturing Practices for Botanical Materials.” *American Herbal Products Association (AHPA)*, Mar. 2017, [http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Documents/AHPA\\_Good\\_Agricultural\\_Collection\\_Practices\\_Good\\_Manufacturing\\_Practices\\_Botanical\\_Materials.pdf?ver=2017-03-30-190312-060](http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Documents/AHPA_Good_Agricultural_Collection_Practices_Good_Manufacturing_Practices_Botanical_Materials.pdf?ver=2017-03-30-190312-060).

<sup>79</sup> “Recommendations for Regulators – Cannabis Operations.” *American Herbal Products Association (AHPA)*, 2 Feb 2016, [http://www.ahpa.org/Portals/0/pdfs/AHPA\\_Recommendations\\_for\\_Regulators\\_Cannabis\\_Operations.pdf](http://www.ahpa.org/Portals/0/pdfs/AHPA_Recommendations_for_Regulators_Cannabis_Operations.pdf).

<sup>80</sup> “WHO Global Report on Traditional and Complementary Medicine.” *World Health Organization*, 2019, <https://apps.who.int/iris/bitstream/handle/10665/312342/9789241515436-eng.pdf?ua=1>

<sup>81</sup> Nowak RE. “DSHEA’s failure.”

<sup>82</sup> Australian Government Department of Health Therapeutic Goods Administration. (2018). *Fees and charges: summary - from 1 July 2018*. Retrieved from Therapeutic Goods Administration website: <https://www.tga.gov.au/book-page/non-prescription-medicines-3>

and some of the claims are very general and have little support in scientific, clinical, or cultural literature.<sup>83</sup>

Most countries don't have one single category under which all botanical products are regulated. Instead they are regulated under a number of different categories depending on the herb. Botanical products are most often regulated as over-the-counter drugs, but they also may be regulated as prescription drugs, health foods, supplements, self-medications, and functional foods, or they can be placed in their own separate category.<sup>84</sup> Given the complex chemical makeup of herbs, and the wide range of safety profiles and therapeutic effects, it makes sense to build flexibility into how a botanical product is regulated.

## TIERED SYSTEMS

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A useful metric for establishing the appropriate regulatory category for a particular herb could be based on an assessment of both the safety profile and hypothetical use cases for a product. This assessment would take into account historical evidence, scientific evidence, reported adverse effects, and pharmacological data, as well as traditional uses and folklore. Does an herbal product make explicit health claims? How strong is its safety profile? For how long has it been used therapeutically and by whom?

Some countries create tiers of products based on a number of factors. Australia, for example, has a two-tier system based on risk. Higher risk medicines must be evaluated for safety and efficacy and registered by the Australia Register of Therapeutic Goods. Lower risk medicines must contain pre-approved, low-risk ingredients, can only make limited claims, and may or may not be listed in the Register. The difference between 'registered' and 'listed' is key -- they have separate requirements and imply different levels of regulatory rigor.

Korea has enacted a four-tiered labeling system for Health/Functional Foods (HFFs), which include supplements and other processed foods. The system is intriguing and worthy of consideration as a model for how it evaluates the safety and veracity of claims made about specific HFFs. Korea requires labels to reflect the quality of evidence supporting the therapeutic use of a product. There are four levels, each with a permitted statement that must be included on the label. Korea's decision-tree of questions for determining product quality, safety and efficacy -- which recognizes the validity of various kinds of data -- might be a useful tool for crafting CBD and cannabis regulations in the United States [see Figure 22.1 in citation].<sup>85</sup>

One of the strengths of this four-tiered system of regulation is that it embodies a more nuanced and realistic view of botanical medicine than the FDA's all-or-nothing approach to sanctifying medical claims. CBD isn't a medicine unless the FDA says it is, according to the FDA, and because whole plant CBD-rich cannabis, unlike pharmaceutical CBD, is not an FDA-approved remedy, artisanal CBD-rich product-makers

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<sup>83</sup> Han, Esther. "Softens Hardness!: TGA under Fire for Health Claim List That Critics Say Endorses Pseudoscience." *The Sydney Morning Herald*, The Sydney Morning Herald, 13 Feb. 2018, [www.smh.com.au/healthcare/softens-hardness-tga-under-fire-for-health-claim-list-that-endorses-pseudoscience-20180207-h0vfst.html](http://www.smh.com.au/healthcare/softens-hardness-tga-under-fire-for-health-claim-list-that-endorses-pseudoscience-20180207-h0vfst.html).

<sup>84</sup> World Health Organization. (2005). *National policy on traditional medicine and regulation of herbal medicines*. Retrieved from World Health Organization website: <https://apps.who.int/medicinedocs/en/d/Js7916e/>

<sup>85</sup> See Kim, J, et al. "Regulations on Health/Functional Foods in Korea." *Nutraceutical and Functional Food Regulations in the United States and Around the World*. Bagchi, Debasis. Elsevier, 2014. pp 389-400.

run afoul of the law if they make health claims about their formulations. This puts cannabis companies and CBD start-ups in an odd position – they have to market their products without saying what they’re good for.

## COURSE CORRECTION

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Since its inception in 1973, the FDA has served as a handmaiden for cannabis prohibition, a dishonest, ignominious policy that has undermined medical science and thwarted medical advances. The FDA has been on the wrong side of history on this issue. Now the FDA has a chance to make a significant course correction by restoring cannabis to its rightful place in the pantheon of therapeutic herbs.

Toward this end, Project CBD recommends the formation of a Committee on Traditional Herbal Medicinal Products to advise the FDA and oversee implementation of a tiered regulatory program. This committee would set separate standards for different kinds of traditional herbal medicines, while validating CBD product safety and quality, which sensible regulations and realistic enforcement policies can ensure without engaging in expensive, drawn-out clinical trials.

The need for better oversight of cannabis products and other herbal supplements is inarguable. The overriding objective should always be easy public access to diverse and affordable product options that are subject to rigorous manufacturing and compliance oversight.