Kansas Bureau of Investigation

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Testimony in Opposition to House Bill 2244
Before the House Standing Committee on Judiciary

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Chairman Patton and Members of the Committee:

My name is Katie Whisman and I serve as the Executive Officer for the Kansas Bureau of Investigation. Thank you for the opportunity to testify in opposition to House Bill 2244, which proposes to legalize cannabidiol (CBD) preparations that contain up to 5% tetrahydrocannabinol (THC).

While there is little doubt that there is tremendous suffering imposed upon those afflicted with debilitating conditions, including those that produce seizures, the details of this bill make the use of CBD oil treatments much broader in application. Before I speak to the policy issue before you, I'd like to provide some general scientific and legal information on marijuana, CBD, and THC that I think may be helpful.

Marijuana refers to the dried leaves, flowers, stems, and seeds from the *Cannabis* plant. While different research publications provide varying numbers, studies over the past decade have identified more than 100 cannabinoids[1], which are naturally occurring chemical compounds unique to the *Cannabis* plant.

Cannabinoids are most abundant in the flowering tops, resin, and leaves of the plant.[2] THC and CBD are two of the most abundant cannabinoids.

- Delta-9-tetrahydrocannabinol is the main psychoactive chemical compound in marijuana. It is a Schedule I controlled substance according to both the Kansas Uniform Controlled Substances Act and the federal Controlled Substances Act.

[1] Mariotti, K.C., et al., Seized cannabis seeds cultivated in greenhouse: A chemical study by gas chromatography-mass spectrometry and chemometric analysis, *Science and Justice*, 56 (2016) 35-41.
[2] DEA Diversion Control Division, *Clarification of the New Drug Code 7350 for Marijuana Extract,* available at https://www.deadiversion.usdoj.gov/schedules/marijuana/m_extract_7350.html. Visited 12/15/2017.

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- CBD is reportedly considered to be non-psychoactive. It *is not* considered a controlled substance in Kansas[3] but it is considered a Schedule I controlled substance according to the federal Controlled Substances Act.

For several years, this legislature has heard pleas from individuals and families seeking relief from debilitating medical conditions, primarily seizure disorders, through legislatively authorized access to CBD outside of United States Food and Drug Administration (FDA) approval. Each year, the proponents claimed it was the CBD, *not* THC that brought relief. This legislature has responded to those pleas on two occasions within the last two years.

In 2017, the Kansas Legislature *prospectively* made cannabidiol, when comprising the sole active ingredient of a drug product approved by the FDA, a Schedule IV drug. In anticipation of the FDA's approval of Epidiolex, this legislation ensured that Epidiolex could be prescribed to Kansas residents as soon as it was approved by the FDA, thus preventing a delay pending the passage of future legislation amending the Kansas Uniform Controlled Substances Act. On June 25, 2018, Epidiolex, the first prescription pharmaceutical formulation of highly-purified, plant-derived CBD was approved by the FDA for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years or older.

In 2018, the Kansas Legislature exempted cannabidiol from the definition of "marijuana" in both K.S.A. 65-4101 and K.S.A. 21-5701, which are the definition sections governing controlled substances and crimes involving controlled substances, respectfully. These exemptions effectively made CBD a product that can be purchased online or over-the-counter in retail outlets across the state.

The combined result of the legislative action in both 2017 and 2018 provided what it was that individuals and families had sought – both the ability to be prescribed a pharmaceutical grade plant-derived CBD or obtain CBD for use without a prescription.

In the first attachment to my testimony, *The Trouble with CBD Oil*, is a paper intended to generate a better understanding of the benefits versus the risks of the current way CBD products are produced, used, and advertised. As explained in this article, CBD oil is essentially a concentrated solvent extract made from cannabis flowers or leaves that is dissolved in an edible oil such as sunflower, hemp, or olive oil. Of particular note are the following excerpts from the paper:

> "Solvents used can vary from relatively innocuous organic solvents (ethanol, isopropyl alcohol) to more harmful ones (petroleum-ether, naphtha), or even super-critical fluids (butane, CO2)."
>
> "It is well known that cannabis plants obtained from uncontrolled sources may be contaminated with various harmful substances, sometimes leading to severe health issues or hospitalization. Contaminants include chemicals that were intentionally added in order to increase yield, weight, or potency (e.g., pesticides, metal particles,

[3] 2018 Kansas Senate Bill 282, which became effective on May 24, 2018, exempted cannabidiol from the definition of "marijuana" in both K.S.A. 65-4101 and K.S.A. 21-5701.

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synthetic cannabinoids) but also agents that entered the plant unintentionally (e.g., heavy metals, molds and bacteria, aflatoxins)... One contaminant specifically relevant to cannabis (CBD or THC) oils is the residual presence of toxic solvents used during the extraction procedure."

In the second attachment to my testimony, *Labeling Accuracy of Cannabidiol Extracts Sold Online,* the identification of present but unlabeled cannabinoids was examined. The following were noted in the article:

- Of the products purchased online, 26% contained less CBD than labeled, which could negate any potential clinical response;
- Actual CBD content was negligible or less than 1% of the labeled content;
- THC content observed may be sufficient to produce intoxication or impairment, especially among children.

While HB 2244 includes requirements for "third-party, independent laboratory" testing, there are no accreditation standards for those entities, no testing requirements specified, nor are there product safety assurances guaranteed. The conclusions one can draw from these articles is that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy and safety of these consumer products, especially when proposing to provide them to children.

While CBD can already be purchased legally in Kansas despite the concerns noted above, HB 2244 also proposes to expand the law and legalize CBD preparations to contain up to 5% THC.

- In a 12.0 ounce bottle of sesame oil containing 5% THC, there would be over 1,600 10mg doses of THC. **Just 1ml of sesame oil would contain 4.6 10mg doses of THC, meaning a few drops would be equivalent to a recreational dose.**

- **The average potency of marijuana in 1980 was 3%.** To put this in context, an average hand-rolled marijuana cigarette weighs about 0.4 gram; at a potency of 3% THC, each hand-rolled marijuana cigarette contains approximately 12 mg THC. This dose produces intoxicating effects and **HB 2244 proposes to nearly double the THC concentration and make it legal to provide to children.**

While HB 2244 was reportedly modeled after Alabama's "Leni's Law", of important note is that Alabama law limits the THC level to *no more than 3% relative to CBD*. This means that if the oil contained 10% CBD there could only be 0.3% actual THC. In no case could CBD oil contain more than 3% THC. It is noteworthy that while evidence suggests it is the CBD that can produce therapeutic results at certain concentrations, **neither HB 2244 nor Leni's Law established minimum CBD concentrations**, yet established THC maximum concentrations. Given this, one must question the true intent of these pieces of legislation.

Given the THC concentration threshold proposed by HB 2244, there would be a certain impact to the KBI Forensic Laboratory. We do not currently have validated methods or specialized laboratory equipment required to perform THC quantitation analysis. Therefore, newly developed methods would have to be validated and specialized analytical equipment and supplies would be required. The minimum fiscal impact anticipated by the KBI in FY 2020 is $257,860. In terms of impact to Forensic Laboratories, the use of a relative

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concentration measurement minimizes the need for additional equipment and development of validated methods of testing.

In closing, I'd like to share with the Committee a conversation I had with Alabama Representative Mike Ball, who sponsored Leni's Law. As fellow law enforcement professionals, we had a respectful telephone conversation last week about his desire to provide relief to people suffering from debilitating conditions. Representative Ball made it explicitly clear that Leni's Law was only a "stop-gap measure" that provided immediate access of CBD/THC to suffering individuals but it was never his intent for it to be "the end game". Representative Ball is currently working to expand access by introducing medical cannabis legislation modeled after Kentucky; it is noteworthy that this legislation as he described it to me bears a striking resemblance to Kansas HB 2163 and SB 113, the veteran's first medical cannabis act.

HB 2244 would bypass the safeguards established by the Food and Drug Administration to protect the public from dangerous and/or ineffective drugs, and, through the legalization of a relatively high amount of THC, opens the door to the legalization of marijuana and THC. As you contemplate the implications of HB 2244, I respectfully ask that you consider the underlying intent of this legislation. Are we exploiting suffering families in the interest of the underground cannabis lobby who seeks to slowly erode controlled substance laws with the ultimate goal of recreationalizing cannabis?

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The Trouble with CBD Oil

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Abstract
In just a few years, cannabidiol (CBD) has become immensely popular around the world. After initially being discovered as an effective self-medication for Dravet syndrome in children, CBD is now sold and used to treat a wide range of medical conditions and lifestyle diseases. The cannabinoid CBD, a non-psychoactive isomer of the more infamous tetrahydrocannabinol (THC), is available in a growing number of administration modes, but the most commonly known is CBD oil. There are currently dozens, if not hundreds, of producers and sellers of CBD oils active in the market, and their number is increasing rapidly. Those involved vary from individuals who prepare oils on a small scale for family and (Facebook) friends to compounding pharmacies, pharmaceutical companies, and licensed cannabis producers. Despite the growing availability of CBD, many uncertainties remain about the legality, quality, and safety of this new "miracle cure." As a result, CBD is under scrutiny on many levels, ranging from national health organizations and agricultural lobbyists to the WHO and FDA. The central question is whether CBD is simply a food supplement, an investigational new medicine, or even a narcotic. This overview paper looks into the known risks and issues related to the composition of CBD products, and makes recommendations for better regulatory control based on accurate labeling and more scientifically supported health claims. The intention of this paper is to create a better understanding of the benefits versus the risks of the current way CBD products are produced, used, and advertised.

What Is CBD Oil

Cannabidiol (CBD) oil is essentially a concentrated solvent extract made from cannabis flowers or leaves that is dissolved in an edible oil such as sunflower, hemp, or olive oil. Solvents used can vary from relatively innocuous organic solvents (ethanol, isopropyl alcohol) to more harmful ones (petroleum-ether, naphtha), or even supercritical fluids (butane, CO_2). The exact conditions and solvents applied have a great impact on, for example, the taste, color, and viscosity of the final product. Because many other plant components are co-extracted with the desired cannabinoids present in the herbal material, these are sometimes removed by a treatment known as "winterization." By placing the extract in a freezer (–20 to –80 °C) for 24–48 h, components with a higher melting point such as waxes and triglycerides, as well as chlorophyll will precipitate, so they can be removed by filtration or centrifugation [1]. This treatment can significantly improve the taste and color of the final product.

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Cannabis oils may contain various concentrations of CBD, tetrahydrocannabinol (THC), and minor cannabinoids, mainly depending on the cannabis variety used for extraction. The most popular product currently is CBD oil, but for example cannabigerol (CBG)-rich oil has been spotted as well [2], and others will very likely follow soon. The THC-rich type of cannabis oil has already been known for some years, and is generally known under the name "Simpson oil" [3]. Terpenes may or may not be present in these products, depending on the preparation method used [4]. Because they are highly volatile, elevated temperatures (such as those applied during drying of plant materials, or during the evaporation of solvents) may result in a significant loss of terpene components [5]. However, it is possible to capture evaporated terpenes by condensation, and reintroduce them back into the final oil. Additional ingredients may be added to further adjust properties such as color, viscosity, taste, or shelf-life stability.

Oil has become a favorite mode of administration for many medical users of cannabis and cannabinoids for multiple reasons. First of all, concentrated extracts allow the consumption of a large dose of cannabinoids in an easily ingestible form. With CBD oil, there is no risk of intoxication (getting high) [6], so much larger doses can be consumed than would be possible for THC-rich products. Many users who prefer the holistic approach of using herbal cannabis worry about the stigma associated with the typical smell caused by smoking or vaporizing it. Cannabis oil has no smell that may identify a consumer as a cannabis user, and it can be used discretely even in a social setting, e.g., at work or around family. Moreover, it can be efficiently dosed simply by counting the number of drops consumed. These same benefits of using a concentrated extract were identified in a large survey among medicinal cannabis users published in 2013 [7], perhaps as an early indicator of the emergence of cannabis oils as a preferred method of ingestion. Currently, the market is developing further towards more sophisticated and patentable products, including oral capsules, liposomal products, skin creams, and chewing gums containing CBD.

Therapeutic Effects of CBD

Today, CBD is used for the treatment of a wide range of medical conditions. This started with the somewhat serendipitous discovery (by parents experimenting with self-medication for their children) that CBD had a therapeutic effect on a serious form of epilepsy in children, called Dravet syndrome [8]. This effect is now under clinical investigation with the pharmaceutical CBD product Epidiolex®, which is currently in phase 3 trials with encouraging results [9, 10]. The media attention generated by its effect on severely ill children gave CBD the push needed to become a much desired medicine almost overnight [11]. Other medical indications that may be treated with CBD, and are supported to some extent by clinical proof, include Parkinson's disease [12], schizophrenia [13], and anxiety disorder [14]. However, although research into the therapeutic effects of CBD is rapidly increasing, most current uses of CBD are not (yet) supported by clinical data. The popular use of these products means that physicians may be confronted with the effects of CBD oil even when they do not prescribe it themselves.

An excellent example is the use of CBD (and also THC) products for the self-medicating of cancer, with the intention of fully curing it [15]. This is based on an increasing body of preclinical evidence showing cannabinoids to be capable, under some conditions, of inhibiting the development of cancer cells in vitro or in vivo by various mechanisms of action, including induction of apoptosis, inhibition of angiogenesis, and arresting the cell cycle [16]. This is certainly exciting news, and research is ongoing around the world, but there is no solid clinical evidence yet to support that cannabinoids – whether natural or synthetic – can effectively and safely treat cancer in actual humans [17]. In fact, there are indications that certain types of cancer may even accelerate when exposed to cannabinoids [18]. This becomes problematic when patients choose to refuse chemotherapy treatment because they firmly believe in the rumored curative properties of cannabinoids. As a result, recommendation of cannabinoids for treating cancer should be done with great care, and with distinction as to the type of cancer being treated [19].

Increasingly, CBD oil is also being promoted as a prophylactic treatment in order to prevent certain diseases from developing at all. The argument used is that the human endocannabinoid system is involved in basic life functions such as appetite, immune response, reproduction, and pain management [20]. Because CBD functions as an indirect antagonist to human CB_1 and CB_2 receptors [21], it is reasoned that the presence of CBD prevents them from being overly activated, thereby protecting the nervous and immune systems from everyday stress. Furthermore, CBD is known to be a reasonably potent antioxidant, which further helps to protect against stressful

influences [22]. Although this clearly increases the market for CBD products, it also further erodes the scientific basis for the therapeutic use of CBD. After all, it is hard to prove scientifically that a disease was prevented by the use of a health-promoting product.

If CBD oil was used mainly by adult, well-informed, and reasonably healthy consumers, the impact of its widespread use would perhaps be quite acceptable and limited. However, this is not the case, as CBD is actively marketed for use by children (e.g., for Dravet syndrome, ADHD, autism), elderly people (Alzheimer's disease, dementia, Parkinson's disease), patients suffering from complex diseases (cancer, multiple sclerosis, chronic pain), and even pets (anxiety, appetite, sleep). Indiscriminate use of CBD may lead to various issues among these consumers. For example, CBD shows an exciting potential for treating epilepsy in children, but the long-term effects of high-dose CBD on these children's brain functions remain unclear, while there are strong clues that the endocannabinoid system is central in the proper neuronal development of the adolescent brain [23]. In order to halt the unchecked advertising of CBD products, health authorities in various countries have begun sending official warning letters to stop producers and sellers from making unfounded health claims [24, 25].

Legal Status of Hemp and CBD

The CBD present in oils and other products is usually derived from fiber-type varieties of cannabis (hemp), because these are naturally higher in CBD content than drug-type varieties (marijuana). Although cultivation of hemp is allowed in many countries around the world, this is usually governed by strict regulations. After being banned for decades, hemp cultivation in the USA has only recently been reintroduced, and is still gearing up for full industrial production [26].

In the European Union (EU), the cultivation of certain cannabis varieties is granted provided they are registered in the EU's *Common Catalogue of Varieties of Agricultural Plant Species* [27] and the THC content does not exceed 0.2% of the dried flowers of the plant [28]. In Canada, hemp is allowed to contain 0.3% THC [29], while Switzerland allows up to 1% THC [30]. In most countries, viable seeds for planting may be purchased from certified seed companies only, in order to make sure that the correct hemp variety is indeed being cultivated. Additionally, hemp may typically only be grown in agricultural fields outdoors, while indoor cultivation is usually forbidden. In some countries (e.g., The Netherlands), growing hemp is allowed only with the intent to produce fibers or seeds. As a result, the act of harvesting fiber cannabis for its CBD is a violation of narcotics laws [31]. New cannabis varieties (for example developed to yield a higher content of CBD) are not (yet) registered as approved hemp varieties, and therefore cannot be freely cultivated, while the official registration process takes several years to complete.

The legal status of CBD in the USA is extra complicated, because many individual states have introduced their own medicinal or even recreational cannabis laws, while the Federal Government does not accept any consumption of cannabis [32]. In the USA [33], but also in Germany and the UK [34], CBD has been technically classified as a new medicine, requiring manufacturers to meet much stricter safety, quality, and effectiveness standards. The statement that CBD is simply "legal in all 50 US states" is therefore misleading, if not untrue. It should be noted that even in places where CBD is technically illegal, products may still be easily available because the authorities are lax about enforcing the law, or discussions are still ongoing on how to deal with the influx of CBD. In short, whether CBD is legal depends of how it was made, what is in the final product, and where you are located.

An important issue in the discussion around cannabis-derived oils is: how much THC is a legal CBD product allowed to contain in order not to be considered a narcotic? Authorities sometimes choose to deal with these regulations in a pragmatic way, recognizing that laws once designed to control marijuana abuse may not be fully applicable to hemp. For example, in the Netherlands, a maximum level of 0.05% THC is allowed in CBD products, even though, formally, any detectable trace of THC is illegal according to Dutch narcotics laws. This approach is based on the fact that even hemp varieties of cannabis produce a small amount of THC, and therefore naturally derived CBD extracts will carry some THC in the final products.

The fact that the maximum CBD content in an oil is limited by the THC present in the herbal material used makes it attractive to add an additional amount of purified CBD to boost the percentage advertised on the label. Unfortunately, the Novel Food Catalogue of the EU states that "extracts of *Cannabis sativa* L. in which CBD levels are higher than the CBD levels in the plant source are novel in food" [35]. This means that enriching a natural hemp extract with pure (often synthetic) CBD makes it a Novel Food product, with the consequence that it must undergo significant safety assessment prior to being mar-

keted. However, it is still unclear in many EU countries if extracts with no added CBD also fall under this regime.

Given the many restrictions and conditions, it can be difficult to set up a fully legal and functional pipeline for the production and sale of CBD oil. Because different countries allow different activities with regards to cultivation, processing, extracting, etc., of hemp, entrepreneurs have often set up production pipelines that span multiple countries, where hemp is cultivated in one country, while extraction takes place in another, lab testing in a third, and sales take place in yet another country. This obviously makes it harder to determine exactly where a CBD product comes from, who is responsible for its final quality, and what standards were followed. For that reason, thorough analytical testing of final products by certified third-party labs is an essential tool to guarantee the safety and composition of CBD oils.

Identifying the Real Risks

The discussion on the legal status of CBD revolves mainly around the question: is it a medicine or a natural food supplement? The main difference is that medicinal drugs are considered unsafe until proven safe, whereas food supplements are considered safe until proven otherwise. As a result, the central question becomes whether or not CBD is safe for consumers (children, elderly, patients) in large and unregulated quantities. Although there is only limited knowledge about the long-term effects of chronic use, or about drug-drug interactions between CBD and other medications [36], human studies have indicated that CBD is very well tolerated even up to a daily dose of 1,500 mg [37]. Indeed, a recent World Health Organization (WHO) review concluded that "to date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD" [38]. However, the risks to be assessed about CBD products may not have much to do with the pure compound CBD itself, but more with the unknown composition and quality of the products offered. In particular, we should be looking into the presence of contaminants in these concentrated extracts, and into incorrect or even misleading labels for the cannabinoid content of products.

It is well known that cannabis plants obtained from uncontrolled sources may be contaminated with various harmful substances [39], sometimes leading to severe health issues or hospitalization [40]. Contaminants include chemicals that were intentionally added in order to increase yield, weight, or potency (e.g., pesticides, metal particles [41], synthetic cannabinoids [42]) but also agents that entered the plant unintentionally (e.g., heavy metals, molds and bacteria [43], aflatoxins). For example, pesticides are frequently present in cannabis sold by Dutch coffee shops [44], but were also found in cannabis offered under state law in California [45] as well as medicinal cannabis from licensed producers in Canada [46]. If any of these contaminants were present in hemp used for CBD extraction, they would likely end up in a concentrated form in the final oil. One contaminant specifically relevant to cannabis (CBD or THC) oils is the residual presence of toxic solvents used during the extraction procedure [3].

Although contaminants come in various shapes and forms, most are relatively easy to detect, because many professional analytical labs exist that routinely screen for such contaminants in, for example, food crops, imported medicinal plants, or edible oils. The standard lab methods, as described in Pharmacopoeia monographs (e.g., USP, EP) or food regulations, could simply be applied to CBD oils, after some minor validation studies. For example, the detection of heavy metals or pesticides present in CBD oil does not significantly differ from the same analysis in, say, a shipment of olive oil. The only analysis that is not yet standard procedure in most analytical labs is the quantification of cannabinoids. Because cannabinoids are only found (with few exceptions [47]) in the cannabis plant, specific analytical methodology must be developed to properly determine the cannabinoid composition of the many CBD products available.

Although a range of analytical methods have been published in recent years [48], there is no general agreement on which analytical method is most suitable and accurate. Additionally, there are currently no generally accepted guidelines or certifications to determine the qualifications of cannabis labs. As a result, cannabinoid analysis can differ significantly between labs [49], even when the exact same sample is analyzed multiple times [50]. This not only poses a risk to consumers (who do not know how trust the label on their product) but may also lead to business-to-business conflicts about the quality or value of intermediate products. Additionally, inaccurate analytical results may lead to legal problems if the THC content of a CBD product unexpectedly turns out to be higher than the maximally allowed limit. It seems clear that a better agreement on the conditions for lab testing of cannabinoids is urgently needed.

Table 1. Analysis of Dutch cannabis oil samples obtained from actual patients, comparing the claimed cannabinoid content on the product label with lab results measured in the study [51]

Sample ID	CBD(A)			THC(A)		
	label, %	measured, %	deviation, rel. %	label, %	measured, %	deviation, rel. %
1	**27**	2.3	*-91.5*	**17**	0.1	*-99.4*
2	**25**	0	*-100*	**35**	4.6	*-86.9*
3	**12**	0.2	*-98.3*	–	0	*
4	**10.9**	2.8	*-74.3*	–	0.1	*
5	**10**	2.2	*-78*	**10**	4	*-60*
6	**8**	0.6	*-92.5*	**4**	0.2	*-95*
7	**8**	0.6	*-92.5*	**4**	0.1	*-97.5*
8	**6**	0.2	*-96.7*	**5**	0.1	*-98*
9	**5**	0	*-100*	**40**	3.4	*-91.5*
10	**4**	4.7	*+17.50*	–	0.2	*
11	**4**	5.4	*+35*	–	0.3	*
12	**4**	4	*0*	–	0	*
13	**4**	4.2	*+5*	–	0	*
14	**3**	3.1	*+3.3*	–	0.2	*
15	**2.75**	2.8	*+1.8*	–	0.1	*
16	**0.1**	0.1	*0*	**4**	6.3	*+57.5*
17	–	0.1	*	**7**	7.9	*+12.9*
18	–	0	*	**5**	0.7	*-86*
19	–	0	*	**5**	0.9	*-82*
20	–	0.1	*	**20**	15.8	*-21*
21	–	0	*	**7**	6.4	*-8.6*

CBD, cannabidiol; THC, tetrahydrocannabinol; CBD(A), total sum of CBD plus CBD-acid; THC(A), total sum of THC plus THC-acid. * Not applicable because no label claim was made.

What Studies Tell Us

Recently, an interesting study performed in the Netherlands highlighted multiple issues that may be extrapolated to CBD products elsewhere [51]. In this study, 46 different cannabis oil samples were collected directly from patients and analyzed for cannabinoid content. The obtained samples were home-made ($n = 29$) or purchased from a (web) store ($n = 17$). For 21 of the 46 products (46% of all samples), label information was available on CBD/THC content, so that the claimed content could be compared to the analyzed content as determined in the study. Results are shown in Table 1. In many cases the analyzed cannabinoid content strongly differed from the claimed content on the label, while in 7 samples no cannabinoids (CBD or THC) were found at all. Such deviations were found in home-made as well as commercially obtained products.

Additionally, as many as 26/46 samples (57%) had a THC content >1%, with one sample peaking at 57.5%. In 18/46 samples (39%) the oil contained virtually only THC (with CBD <0.1%). Although many of the samples analyzed were purposely made to contain a high THC content, it is unclear whether oil consumers are always aware they are consuming THC, and thereby exposing themselves to the adverse effects of this psychotropic compound, such as intoxication, panic attacks, or disorientation. It should be noted that although the exact legal status of CBD may be debatable, THC-rich extracts are strictly prohibited in virtually all countries.

Another interesting observation was the presence of high levels of non-decarboxylated cannabinoids in multiple samples. It is well known that CBD and THC are not produced as such by the metabolism of the cannabis plant. Instead, cannabinoids are excreted in the form of carboxylic acids such as CBD-acid and THC-acid [52]. The physiological effects of these "acidic" cannabinoids have been studied only to a very limited extent. Only after proper heating (e.g., during smoking, vaporizing, or baking with cannabis) are these natural precursors rapidly

converted into the more well-known CBD and THC, respectively. This process is called decarboxylation [52]. Although decarboxylation also takes place during the production of cannabis oils (e.g., during the evaporation of solvents, or during a separate decarboxylation step as part of the production process), 7/46 samples (15%) contained >25% of its cannabinoid content in the form of acidic cannabinoids, indicating poor control over the decarboxylation process. To address the issue, some producers simply add up the content of CBD and CBD-acid in order to boast a higher "total CBD" content on the label, while advertising this as "raw CBD."

Various studies done on CBD oils and other cannabis products around the world have come to similar conclusions about incorrect label information [24, 53, 54] and the presence of contaminants [54–57]. In the absence of a clear legal status for CBD, or agreement on common safety and quality standards, it may not be surprising that current CBD products leave something to be desired. The time has come for regulators to give CBD the attention it deserves in order to ensure that affordable, safe, and reliable CBD products are available to those who depend on them.

Conclusion

Almost overnight, CBD oils have become an interesting combination of popular holistic medicine, miracle cure, and a natural answer to the synthetic drugs dominating modern medicine. With CBD, patients receive the promise of being in control of their own ailments, and no longer feeling at the mercy of their treating physicians. This has turned out to be a particularly powerful message. Many patients use CBD oils freely for ailments both confirmed and self-diagnosed, and the rapid innovations with CBD products have actually been quite impressive. But while new CBD products keep entering the market virtually unchecked, effective regulatory control of these products has stayed far behind. As a result, unknown risks about long-term effects remain unaddressed, especially in vulnerable groups such as children, the elderly, and the chronically or terminally ill. It should be noted that this discussion goes well beyond CBD only, as new products containing additional cannabinoids like CBG, THCV, and acidic cannabinoids are following closely behind. We know even less about these compounds than about CBD, and very limited human safety data are available.

Although CBD seems destined to play an important role as a therapeutic agent for a growing number of medical indications, we should seriously ask ourselves if the current unregulated production and sale of CBD oils is done responsibly. Despite the fact that CBD is mainly sold as "just" a food supplement, it is often used by severely ill people with the intention of improving their body functions in a way that their standard medication could not. This obviously puts CBD uncomfortably close to the realm of medicines. Interestingly, the WHO, based on a review of available scientific data and input from international experts, recently concluded that CBD does not immediately require rescheduling as a drug [38], although a fuller review on the risks and benefits of CBD is still being planned. Nevertheless, perhaps the use of CBD products should be assessed in a broader perspective, to cover all ingredients used in the preparation, as well as any contaminants that are already known to be common in recreational cannabis.

Determining risks and benefits through proper clinical trials remains highly desired, but these will take considerable time and funds. As a result, clinical data will not appear any time soon, while patients will not simply stop using the many CBD products to which they have become accustomed. Taking back regulatory control over CBD could therefore start with a more short-term and achievable approach, i.e., demanding accurate and proper labeling, reflecting in detail what each product does and does not contain, and how it was manufactured. For a clearer judgment of the potential therapeutic effects, the risks, but also the legality of a cannabis extract, it is important to know its exact composition. After all, published data from around the world has taught us that misleading labels as well as harmful contaminants are real and actual problems for CBD products. The analytical methodology and the third-party labs needed for this approach largely already exist, and could easily be optimized to quickly get a better grip on the unrestrained cannabinoid market. This approach would hold each producer strictly accountable for the quality and safety of their own products, as long as there are real legal consequences for those businesses that break the rules. Add to this a system for regular professional audits and inspections, and a crackdown on unsubstantiated health claims, and we have a reasonable system to ensure that CBD can be used responsibly by those who need it, until much needed clinical data become available.

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Letters

RESEARCH LETTER

Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.[1] Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inaccurate labeling of some products.[2] To maximize sampling and ensure representativeness of available products, we examined the label accuracy of CBD products sold online, including identification of present but unlabeled cannabinoids.

Methods | Internet searches (keywords: *CBD, cannabidiol, oil, tincture, vape*) were performed between September 12, 2016, and October 15, 2016, to identify CBD products available for online retail purchase that included CBD content on packaging. Products with identical formulation as another product under the same brand were excluded. All unique CBD extracts that met these criteria were purchased. Products were stored according to packaging instructions, or if none were provided, in a cool, dry space. Within 2 weeks of receipt, product labels were replaced with blinded study identifiers and sent to the laboratories at Botanacor Services for analysis of cannabinoid content (cannabidiol, cannabidiolic acid, cannabigerol, cannabinol, Δ-9-tetrahydrocannabinol, Δ-9-tetrahydrocannabibolic acid [THC]) using high-performance liquid chromatography (in triplicate; lower limit of quantification, ≤0.3170% wt/wt). A 10-point method validation procedure was used to determine the appropriate sample preparation and analytical method. Triplicate test results were averaged and reported by product weight. Data were analyzed using SPSS Statistics (IBM), version 23, with descriptive analyses and a 2-tailed χ^2 (α <.05). Consistent with other herbal products in the US Pharmacopeia and emerging standards from medicinal cannabis industry leaders, a ±10% allowable variance was used for product labeling (ie, accurately labeled = 90%-110% labeled value, underlabeled >110% labeled value, and overlabeled <90% labeled value).

Results | Eighty-four products were purchased and analyzed (from 31 companies). Observed CBD concentration ranged between 0.10 mg/mL and 655.27 mg/mL (median, 9.45 mg/mL). Median labeled concentration was 15.00 mg/mL (range, 1.33-800.00). With respect to CBD, 42.85% (95% CI, 32.82%-53.53%) of products were underlabeled (n = 36), 26.19% (95% CI, 17.98%-36.48%) were overlabeled (n = 22), and 30.95% (95% CI, 22.08%-41.49%) were accurately labeled (n = 26) (**Table 1**). Accuracy of labeling depended on product type [$\chi^2(1) = 16.75$; $P = .002$], with vaporization liquid most frequently mislabeled (21 mislabeled products; 87.50% [95% CI, 69.00%-95.66%]) and oil most frequently labeled accurately (18 accurately labeled products; 45.00% [95% CI, 30.71%-60.17%]). Concentration of unlabeled cannabinoids was generally low (**Table 2**); however, THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested (21.43% [95% CI,

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36) [380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

[a] Cannabidiol content tested within 10% of labeled value.

[b] Cannabidiol content exceeded labeled value by more than 10%.

[c] Cannabidiol content tested more than 10% below labeled value.

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

	Average Observed Concentration Across Tests, mg/mL	
Cannabinoid	Mean (SD)	Median (Range)
Cannabidiol[a]	30.96 (80.86)	9.45 (0.10-655.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.08 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ-9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ-9-Tetrahydrocannabibolic acid	0	0

[a] The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

14.01%-31.35%]), cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

Discussion | Among CBD products purchased online, a wide range of CBD concentrations was found, consistent with the lack of an accepted dose. Of tested products, 26% contained less CBD than labeled, which could negate any potential clinical response. The overlabeling of CBD products in this study is similar in magnitude to levels that triggered warning letters to 14 businesses in 2015-2016 from the US Food and Drug Administration[3] (eg, actual CBD content was negligible or less than 1% of the labeled content), suggesting that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy of these consumer products. Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses[4,5]; however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children.[6] Although the exclusive procurement of products online is a study limitation given the frequently changing online marketplace, these products represent the most readily available to US consumers. Additional monitoring should be conducted to determine changes in this marketplace over time and to compare internet products with those sold in dispensaries. These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.

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Author Contributions: Dr Bonn-Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bonn-Miller, Loflin, Thomas, Vandrey.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bonn-Miller, Loflin, Marcu, Vandrey.
Critical revision of the manuscript for important intellectual content: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.
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Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications

A major aim of trial registration is to help identify and deter the selective reporting of outcomes based on the results.[1,2] However, it is unclear whether registered outcomes accurately reflect the trial protocol and whether registration improves the reporting of primary outcomes in publications. We evaluated adherence to trial registration and its association with subsequent publication and reporting of primary outcomes.

Methods | We conducted a cohort study of all initiated clinical trial protocols approved in 2007 by the research ethics committee for the region of Helsinki and Uusimaa, Finland. Registry records and articles published up to February 2017 were identified using keywords to search trial registries, PubMed, EMBASE, Cochrane Central, Finnish databases (Medic, ARTO, TUHAT), and Google. Trial characteristics and outcomes were extracted in duplicate from each protocol (including amendments), registry record, and publication.

Using descriptive statistics and multivariable logistic regression adjusting for characteristics in **Table 1**, we determined