

## Introduction

On behalf of the National Cannabis Industry Association (NCIA), and in response to the U.S. Food and Drug Administration (FDA) request for comments on Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds, published in the April 3, 2019 edition of the Federal Register, we hereby submit public comments.

In addition to our specific expertise, and on behalf of NCIA members and the cannabis and cannabidiol (CBD)/hemp industries at large, we have formed a coalition of CBD/hemp entrepreneurs, scientists, medical professionals, and food and drug lawyers to provide public comment to the FDA and to answer specific questions posed by the FDA, to provide general context about the industry, and to highlight relevant work that we have previously done on packaging, labeling, and lab testing that could inform FDA rulemaking.

Given the substantial interest in this topic and the need for regulations and standardization throughout the industry, NCIA and this coalition are providing specific insight into all facets the FDA would like to examine, including health and safety risks, manufacturing and product quality, and marketing, labeling, and sales.

Hemp-derived CBD is in high demand by consumers, and the industry is eagerly awaiting the FDA's regulatory framework for these products. Our industry coalition firmly believes that by working in partnership with the FDA to inform rulemaking, we can develop an appropriate regulatory framework to ensure the safety and efficacy of these important products.

### **The Economic Benefits of a Robust CBD and Hemp Industry**

The hemp-derived CBD industry's highest priority is product safety, and we will address this issue in the bulk of our submission. However, the economic impact of this nascent industry cannot be ignored. When the 2018 Farm Bill was signed into law on December 20, 2018, it ushered in the potential for a new agricultural industry that will have impacts in textiles, building materials, paper, energy, pharmaceuticals, dietary supplements, and countless other consumer products.

Current research indicates that at present, about seven percent of all adult Americans, or about 22 million people, use CBD as a supplement.<sup>1</sup> The current market size is estimated at between \$600 million<sup>2</sup> and \$2 billion,<sup>3</sup> which includes dietary supplement, pharmaceutical, and food supplement channels. This current economic activity supports between 3,000 and 10,000 direct full-time equivalent jobs and between 10,000 and 35,000 total jobs when considering secondary

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<sup>1</sup> Cowen Research, et al. *Ahead of the Curve: Cowen's Collective View of CBD*, Cowen, Inc. (Feb. 25, 2019), <https://www.cowen.com/reports/cowen-collective-view-of-cbd/>.

<sup>2</sup> *The CBD Report: 2018 Industry Outlook*, Hemp Business Journal (Sept. 2018), <https://www.hempbizjournal.com/market-reports/>.

<sup>3</sup> See *supra* note 1.

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economic impacts.<sup>4</sup> A five-year projection shows a potential \$16 billion domestic market that supports about 82,000 direct jobs and 278,000 total jobs. These figures include jobs across the supply chain, including agriculture, manufacturing, transportation, legal, accounting, and management roles.

These figures represent the observable, industry-related economic potential, but that is not the complete picture. CBD consumers have widely reported health benefits regarding symptoms ranging from arthritis pain to serious seizures, and the economic benefit of the increased productivity of these individuals, and from avoiding more costly treatment options, will be sizable.

The global CBD product market represents another potentially large market opportunity of about \$22 billion by 2022.<sup>5</sup> The United States can be competitive in the international market only with clear and fair domestic regulations. The FDA can foster or stifle these projected benefits based on its approach to regulating the production, manufacture, and sale of extracted hemp products. Above all, there needs to be a transparent and operable system that promotes consumer safety and confidence while also nurturing this significant economic and employment opportunity.

### Importance of Having a Robust Regulatory System

Because safe and effective use of hemp-derived CBD is our industry's goal, we welcome appropriate regulation and oversight by the FDA. We believe in the safety and efficacy of CBD products and that normalizing hemp-derived CBD as a regulated dietary supplement and ingredient in food products, like conventional food and supplements, will enhance product safety and consumer confidence. CBD is one of many cannabinoids found within cannabis to possess therapeutic effects.<sup>6</sup> Under a regulated system, the hemp-derived CBD industry can benefit from

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<sup>4</sup> Estimates derived using standard industry multipliers. Josh Bivens, *Updated employment multipliers for the U.S. economy*, Economic Policy Institute (Jan. 23, 2019), <https://www.epi.org/publication/updated-employment-multipliers-for-the-u-s-economy/>.

<sup>5</sup> *CBD Market Insights*, Brightfield Group, <https://www.brightfieldgroup.com/products/cbd-market-research> (last visited May 21, 2019).

<sup>6</sup> Up until the recent passage of the Farm Bill, all cannabis plants, and cannabis derivatives and extracts, violated the federal Controlled Substances Act (CSA). The CSA established five schedules of controlled substances known as Schedules I, II, III, IV, and V. Schedule I controlled substances are deemed to have a high potential for abuse, possess no currently accepted medical use in treatment, and lack accepted safety for use under medical supervision. Marijuana is identified as a Schedule I substance. Marijuana is defined as all parts of the plant *Cannabis sativa L.*, including the seeds and resin and any compound, manufacture, salt, derivative, mixture, or preparation of such plant. *Cannabis sativa L.* is a broad category, which includes hemp, effectively making the substances derived from hemp illegal under the CSA.

The \$867 billion Farm Bill provides billions in aid to U.S. farmers, but more importantly for cannabis and the cannabis industry, hemp (including its cannabinoids) was exempt from the CSA and is no longer considered a Schedule I substance. Per section 10113 of the Farm Bill, hemp is defined as a cannabis plant containing 0.3 percent or less of tetrahydrocannabinol (THC). Any cannabis plant that contains more than 0.3 percent THC would be considered non-hemp cannabis—or marijuana—under the CSA and lack legal protection under the Farm Bill. Moreover, the Farm Bill allowed for hemp cultivation and the transfer of hemp-derived products across state lines for commercial purposes as well as qualifying it for crop insurance. Regulating hemp cultivation is designed for dual efforts by the United State Department of Agriculture (USDA) and state departments of agriculture. Finally, it

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governmental oversight, maximizing compliance. Currently, hemp CBD products are already being sold in various markets, including retail CBD shops and online. With such a burgeoning market, it is imperative to effectively regulate hemp CBD products, particularly products having a direct impact on public health.

We hope that our submission, along with others being considered, will provide the FDA with the data necessary to establish a regulatory pathway for hemp-derived CBD. At the same time, additional data should be gathered to support the regulatory process. Data gathering and research are being conducted in the private sector, but collaboration with regulators will be necessary to validate the process.

We strongly recommend that the FDA act quickly to clarify the regulatory environment because there is significant confusion in the market. Consumers consistently ask why a federally legal substance is currently prohibited in foods, drugs, cosmetics, and wellness products under FDA regulations. These inquiries will likely remain a source of confusion, especially when so many individuals already use CBD products. In addition, banks, insurance companies, and other professional entities do not currently understand the regulatory landscape, and as a result, many CBD companies are at risk of losing necessary professional services. Because of this, it is critical for the FDA to advance relevant and appropriate regulations to satisfy the health, safety, and security needs of consumers in a timely fashion.

We appreciate that the FDA's current position is that hemp-derived CBD cannot be used as an ingredient in dietary supplements or food.<sup>7</sup> At the same time, we are confident that the FDA will quickly change this position in recognition of the broad use, efficacy, and safety of these products.

In addition, until such time as the FDA issues a new regulation, we recommend that the FDA continue to exercise its enforcement discretion to allow consumers continued access hemp-derived CBD products. We support the FDA's issuing warning letters for drug claims that go

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should be noted that Section 12619 allows any cannabinoid derived from hemp to be considered legal, provided the production meets federal and state regulations.

<sup>7</sup> The FDA has clearly stated its position that such inclusion is unlawful under the Federal Food, Drug, and Cosmetic Act (FDCA). The FDCA, as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), defines a "dietary supplement" as a product intended to supplement the diet that contains one or more of the following: (a) a vitamin; (b) a mineral; (c) an herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (a) through (e). Thus, the law permits a wide range of dietary ingredients in dietary supplements, including CBD, which is an extract of a botanical (*Cannabis sativa L.*). CBD also falls under clause (e) because it is a dietary substance for use by man to supplement the diet by increasing the total dietary intake. The justification is premised on section 301(II) of the FDCA, which prohibits interstate commerce of foods containing an active ingredient in an approved drug, such as Epidiolex (known as IND Preclusion). This position has been communicated through Warning Letters sent to hemp-CBD businesses, along with FDCA Q&A postings. It should be noted that controversy exists with this position. Some have argued that the FDA misinterpreted the Investigational New Drug (IND) Preclusion rule because the FDA believes the preclusion date is the date it authorized CBD as an IND, without giving deference to the remaining portion of the statute, which requires that substantial clinical investigation be commenced and that such substantial clinical investigation be made public.

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beyond substantiated claims and believe that this is the best approach until the FDA issues rules establishing a pathway for regulating food and supplements containing CBD.

### **Significant Issues with Banking and Processing of Transactions**

The FDA recently announced that hemp/CBD for human consumption is not legal without a new drug agreement and clinical trials, because it has now classified CBD as an approved drug. Since that pronouncement, Elavon (U.S. Bank) announced that it would close all merchant accounts because of uncertainty related to health claims being made by some CBD companies, federal/state conflict of laws, and a lack of clarity on how the FDA intends to regulate this industry. Our coalition would like to work with the FDA on an interim fix, clarifying that the FDA intends to allow (or does not intend to pursue action against) the sale of ingestible CBD, as long as there are no disease claims associated with the marketing or labeling of the products. But, we also believe that a legislative fix is desirable, and strongly support the SAFE Banking Act.

The stakes could not be higher for this industry. If we do not succeed in working together to reassure the card brands that they can safely support our industry, then we predict a significant decrease in CBD sales within the next few months. The majority of e-commerce businesses will be forced to conceal the nature of their business, which will inevitably lead to them being discovered during banking audits and likely cause them to be placed on MasterCard's MATCH list of prohibited merchants for transaction laundering. Such a development would prevent a business and its owner from taking credit card payments for five years.

### **Roadmap to the Questions Posed by the FDA**

Below are answers to the various questions posed by FDA in the request for comments on Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds, published in the April 3, 2019 edition of the Federal Register. Based on the questions posed, it is clear that FDA's principal concern is making certain that CBD products are safe. As we explain in greater detail below, an overwhelming preponderance of evidence indicates that cannabis and cannabis-derived compounds, in the course of their normal use in healthy adult consumers, present minimal safety concerns. In the absence of federal requirements, the industry as a whole has been working collaboratively to create standards and best practices to address safety, consistency, and quality when manufacturing cannabis-derived products. We look forward to working with industry to make certain that we are putting our best foot forward. And we look forward to an open dialogue with the FDA as we navigate these new regulatory waters together.

## **Health and Safety Risks**

**1. Based on what is known about the safety of products containing cannabis and cannabis-derived compounds, are there particular safety concerns that FDA should consider regarding regulatory oversight and monitoring of all of these products? For example:**

- **What levels of cannabis and cannabis-derived compounds cause safety concerns?**

Public health and safety should always be a priority and concern when introducing new consumer products into the market, regardless of industry. And certainly, health and safety must be prioritized when considering a regulatory framework for cannabis and cannabis-derived compounds. Fortunately, an overwhelming preponderance of evidence indicates that cannabis and cannabis-derived compounds, in the course of their normal use in healthy adult consumers, present minimal safety concerns.

A study published in *The Lancet* used scientific and medical criteria to determine the relative harm of drugs and established that alcohol, heroin, cocaine, and methamphetamine are far more harmful to individuals and society than cannabis.<sup>8</sup> To date, there are still no reported deaths due to the intoxicating effects of cannabis, while the annual number of deaths from prescription opiates may exceed 63,000.<sup>9</sup> Alcohol-related deaths total approximately 88,000 annually,<sup>10</sup> and the figure for tobacco is 480,000.<sup>11</sup> Another reliable research study that compared the relative risk assessments of alcohol, tobacco, cannabis, and other illicit drugs using the margin of exposure approach showed that cannabis, by a wide margin, is the least risky of these recreational drugs.<sup>12</sup>

The safety of cannabis-derived compounds in isolation has also been evaluated by the federal government. For example, the safety of (–)-*trans*- $\Delta^9$ -tetrahydrocannabinol (THC) and cannabidiol (CBD) in humans, the two chemical components of cannabis most widely used in formulated cannabis products, has been very well established in a large number of FDA-registered clinical studies. A search in the U.S. National Library of Medicine for CBD and THC yields results for over 875 clinical studies.<sup>13</sup>

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<sup>8</sup> David J. Nutt, Leslie A. King, & Lawrence D. Phillips, *Drug harms in the UK: A multicriteria decision analysis*, 376 *Lancet* 1558 (Nov. 1, 2010).

<sup>9</sup> Press Release, Centers for Disease Control and Prevention, U.S. drug overdose deaths continue to rise; increase fueled by synthetic opioids (March 29, 2018), <https://www.cdc.gov/media/releases/2018/p0329-drug-overdose-deaths.html>.

<sup>10</sup> *Alcohol Facts and Statistics*, National Institute on Alcohol Abuse and Alcoholism, <https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics> (last updated Aug. 2018).

<sup>11</sup> *Smoking and Tobacco Use: Fast Facts*, Centers for Disease Control and Prevention, [https://www.cdc.gov/tobacco/data\\_statistics/fact\\_sheets/fast\\_facts/index.htm](https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm) (last reviewed Feb. 6, 2019).

<sup>12</sup> Dirk W. Leachenmeier & Jürgen Rehm, *Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach*, 5 *Sci. Reports* 8126 (Jan. 30, 2015).

<sup>13</sup> U.S. National Library of Medicine, <https://www.clinicaltrials.gov> (last visited May 21, 2019).

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Numerous clinical studies have shown that CBD is safe and well tolerated in humans, even at very high (> 30 mg/kg/day) doses. This dose is approximately equivalent 2,800 mg per day for the average adult male, 2,000 mg per day for the average adult female, and 550 mg per day for the average child. In humans, CBD exhibits no effects indicative of any abuse or dependence potential.<sup>14, 15, 16, 17</sup> To date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD.<sup>18</sup> In a large longitudinal clinical study, the two most common side effects of high-dose CBD (25-50 mg/kg/day) were diarrhea and somnolence, which occurred only in a minority of subjects studied (24% and 30%, respectively).<sup>19</sup>

It should be noted that while the cannabis plant contains hundreds of molecules in addition to THC and CBD (~140 cannabinoids have been identified in cannabis extracts to date),<sup>20</sup> little or no information exists regarding their safety in humans. The plant also contains numerous terpenes and phenolic compounds, including flavonoids, but these compounds are present in cannabis plants at lower levels<sup>21</sup> and are not known to present any major safety concerns. In fact, a correlation has been shown in humans between dietary phenolic compounds and reduced incidence of chronic diseases such as cancer and neurodegenerative diseases.<sup>22</sup> For this reason, cannabis-derived compounds in food may actually be beneficial to human health.

As with any substance that is consumed, large doses can in some instances cause undesirable effects. In cannabis, we've seen a condition recently identified as cannabis hyperemesis syndrome (CHS).<sup>23</sup> CHS is a rare condition that has been diagnosed in a small number of daily,

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<sup>14</sup> Orrin Devinsky, et al., *Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome*, 90 *Neurology* e1204 (Apr. 3, 2018).

<sup>15</sup> Kerstin Iffland & Franjo Grotenhermen, *An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies*, 2.1 *Cannabis Cannabinoid Research* 139 (2017).

<sup>16</sup> Mateus Machado Bergamaschi, et al., *Safety and Side Effects of Cannabidiol, A Cannabis sativa Constituent*, 6 *Current Drug Safety* 237 (2011).

<sup>17</sup> Linda C. Laux, et al., *Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results*, *Epilepsy Research*, Aug. 2019, at 13.

<sup>18</sup> Fortieth Meeting of the Expert Comm. on Drug Dependence, *Cannabidiol (CBD) Critical Review Report* (2018), <https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf>.

<sup>19</sup> Linda C. Laux, et al., *Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results*, *Epilepsy Research*, Aug. 2019, at 13.

<sup>20</sup> Oier Aizpurua-Olaizola, et al., *Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes*, 79 *Journal of Natural Products* 324 (2016).

<sup>21</sup> Christelle M. Andre, Jean-Francois Hausman & Gea Guerriero, *Cannabis sativa: The Plant of the Thousand and One Molecules*, 7 *Frontiers in Plant Science*, no. 19, Feb. 14, 2016, <https://doi.org/10.3389/fpls.2016.00019>.

<sup>22</sup> Ilja C. W. Arts & Peter C. H. Hollman, *Polyphenols and disease risk in epidemiologic studies*, 81 *Am. Journal of Clinical Nutrition* 317S (Jan. 1, 2005).

<sup>23</sup> Neera Khatter & Joanne C. Routsolias, *Emergency Department Treatment of Cannabinoid Hyperemesis Syndrome: A Review*, 25 *Am. Journal of Therapeutics* e357 (2018).

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long-term and heavy users of cannabis and is characterized by nausea, abdominal pain, and severe bouts of vomiting. These symptoms are temporary and subside within a short time after discontinuation of cannabis. Although the exact causes for CHS are not known, it is important to emphasize that this condition is extremely rare relative to the percentage of the population that uses cannabis.<sup>24</sup>

A small number of epidemiological studies have associated long-term cannabis use with mental illness.<sup>25</sup> However, these are all association studies that, by design, could not establish a causal link. We are unaware of any prospective clinical studies examining the potential negative effects of cannabis on mental illness. In contrast, one recent study indicated that CBD might actually benefit children with autism spectrum disorder,<sup>26</sup> and numerous clinical studies of the effects of CBD on autism are now underway.

While cannabis itself may not have been proven to be harmful for humans, there may be safety concerns associated with potential contaminants found in formulated cannabis products. For example, the Centers for Disease Control and Prevention reported that 52 people in Utah were poisoned by an unregulated CBD product, which contained a synthetic cannabinoid.<sup>27</sup> To address potential safety concerns, most states that have legalized the sale of cannabis have enacted strict regulations to ensure that all cannabis products are tested in a licensed analytical laboratory to ensure that dangerous levels of potential contaminants (e.g., residual solvents, pesticides, and heavy metals) are absent from products that are consumed. This coalition believes that the FDA should ubiquitously require that such testing be performed, either in-house or by a third party.

The introduction of terpenes, minor cannabinoids, or other molecules not found in the cannabis plant to formulated cannabis products may also raise some safety concerns. For example, while most cannabis goods on the market contain levels of terpenes similar to those that occur naturally in the cannabis plant, some products contain terpenes at much higher concentrations. High levels of terpenes and other molecules can also occur if chemical procedures such as distillation are used to concentrate THC or CBD from cannabis or hemp oil. In general, terpenes are benign at low concentrations. However, overexposure to concentrated terpenes has the potential to lead to negative effects, including hypersensitive (allergic) reactions in chemically sensitive people.<sup>28</sup> Cannabis manufacturers that make formulated products must ensure that safe levels of any molecules that are introduced into these products, including but not limited to terpenes and minor cannabinoids, are introduced at levels known to be safe for human consumption.

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<sup>24</sup> Joseph Habboushe, et al., *The Prevalence of Cannabinoid Hyperemesis Syndrome Among Regular Marijuana Smokers in an Urban Public Hospital*, 122 *Basic & Clinical Pharmacology & Toxicology* 660 (Jan. 12, 2018).

<sup>25</sup> Koby Coehn, Abraham Weizman & Aviv Weinstein, *Positive and Negative Effects of Cannabis and Cannabinoids on Health*, 105 *Clinical Pharmacology & Therapeutics* 1139 (Jan. 31, 2019).

<sup>26</sup> Marika Premoli, et al., *Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment*, 224 *Life Sciences* 120 (May 1, 2019).

<sup>27</sup> Roberta Z. Horth, et al., *Notes from the Field: Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol - Utah, 2017-2018*, 67 *Morbidity and Mortality Weekly Report* 587 (May 25, 2018), <https://www.cdc.gov/mmwr/volumes/67/wr/mm6720a5.htm>.

<sup>28</sup> Yaqin Pan, William J. Rea & Carolina Restrepo, *Terpenes and Terpenoids in Chemical Sensitivity*, *Alternative Therapies in Health and Medicine*, July 2015, at 12.

- **How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?**

Cannabis is widely consumed in human populations by different modes of delivery, and each mode produces unique and different effects on human physiology, in large part because the pharmacology (e.g., adsorption, distribution, metabolism, and excretion) of cannabis-derived compounds varies depending on the route of consumption.

Inhalation is the most common form of cannabis consumption and is achieved by inhaling the cannabis flower after combustion in a joint, pipe, or water bong. Because THC and many other molecules in cannabis are highly lipophilic, this form of cannabis consumption results in very rapid absorption of these compounds into the bloodstream and brain (within minutes). As such, smokers of cannabis experience physiological changes within minutes of inhaling that include altered senses and euphoria. These effects typically dissipate within 30-90 minutes after inhaling. As described above, the inhalation of cannabis has not been associated with any significant adverse safety issues in humans, despite its widespread use.

While it was originally hypothesized that cannabis might impair lung function similar to the impairment that occurs with the smoking of cigarettes, a large federally funded study found no adverse effects of inhaling cannabis chronically on lung function, and in fact cannabis appeared to protect against the damage of cigarette smoking in people who inhaled both, suggesting that compounds in cannabis might actually improve lung function, perhaps due to their effects on bronchodilation and/or inflammation.<sup>29</sup> Moreover, cigarette smokers typically exhibit much heavier usage than those who inhale combusted cannabis flower, which may relate to the highly addictive nature of nicotine and other molecules found in cigarettes.

“Vaping” is another form of inhaling cannabis oil that is rising in popularity. In this form of consumption, an oil extract from cannabis is placed into an atomizer device that heats the oil, causing it to form a vapor that is then inhaled into the lungs. As with the inhalation of cannabis flower, vaping is associated with rapid onset of cannabis-induced effects because the cannabis molecules are rapidly absorbed into the bloodstream and brain. Inhalation modes, such as vaping, provide more immediate feedback than ingestion, thereby allowing the consumer to better self-titrate/control exposure. There are newer vaping devices already on the market and/or entering the market that claim the ability to control metered doses with resolution in the 0.5 mg to 2.5 mg range. These products will enable consumers to more accurately measure and control their consumption/exposure when compared to combustible and perhaps even ingested modes.

In principle, the vaping of cannabis extracts is considered a safer alternative to inhalation of combusted cannabis flower because it avoids all of the potential carcinogens that are produced upon combustion of cannabis. Nonetheless, some safety concerns related to vaping have arisen. Most of the safety concerns relate to potential contaminants that are found in the cannabis or

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<sup>29</sup> Pletcher, et al., *Association Between Marijuana Exposure and Pulmonary Function over 20 Years*, 307 JAMA 173 (Jan. 2012).

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hemp extracts. For example, in some instances, carcinogenic contaminants like butane (which is sometimes used to make the oil extract) have been identified. Another major safety concern relates to potential contamination due to pesticides used when the cannabis plants are grown. Because these pesticides can be greatly concentrated in the extraction process, they can present a significant health risk to consumers. However, to address the potential safety concerns, most states that have legalized cannabis have enacted strict regulations to ensure that all cannabis vape oils are tested in a licensed analytical laboratory to ensure that dangerous levels of potential contaminants (e.g., residual solvents, pesticides, and heavy metals) are absent from products that are consumed. Again, our coalition strongly supports the FDA in requiring stringent lab testing to make certain that harmful chemicals are not being ingested by consumers.

Some cannabis oils in vape pens contain a mix of propylene glycol and glycerin, similar to that used in the electronic cigarette industry, which can also lead to potential safety concerns. For example, the heating of propylene glycol and glycerin can result in their degradation into glycerinaldehyde, lactaldehyde, dihydroxyacetone, hydroxyacetone, glycidol, acrolein, propanal, acetone, allyl alcohol, acetic acid, acetaldehyde, formic acid, and formaldehyde.<sup>30</sup> The abundance of these decomposition products may depend upon the temperature of the metal heating element but could also depend upon some catalytic aspect of the metal surface. Some high-strength batteries heat the cannabis oil to a very high temperature, which is often far above the melting points of compounds found in cannabis. In certain instances, this has been shown to lead to thermal decomposition of some molecules in cannabis extracts, such as terpenes, resulting in the formation of new molecules with established toxicities.<sup>31</sup> Analytical tests for aerosolized cannabis, similar to those used in the electronic-cigarette industry, should be developed, implemented, and mandated to address such safety concerns.

When considering the vaporization mode of delivery, one should also evaluate the safety of the delivery system itself. The primary safety considerations of electronic vaporizers relate to the battery cell and electrical system. Electronic vaporizers used to aerosolize cannabis oil are substantially similar to, and sometimes identical to, electronic vaporizers used for nicotine delivery. These systems are commonly known as Electronic Nicotine Delivery Systems (ENDS). Historically, some ENDS devices were associated with a risk of fire or explosion. This was primarily due to poor-quality battery cells and inadequate safety features incorporated in certain ENDS devices sold by small manufacturers. Data on the incidence of battery-related fires and explosions related to the use of ENDS devices as well as methods to make ENDS devices safer were presented to the FDA during the Battery Safety Concerns in Electronic Nicotine Delivery Systems (ENDS) Public Workshop conducted in April 2017. Subsequently, standards have been developed to guide the improvement in safety of ENDS devices, including ANSI/CAN/UL 8139, Standard for Safety of Electrical Systems of Electronic Cigarettes. The adoption of such standards in the design of ENDS devices should result in an electrical risk profile similar to that of other mass-produced consumer electronics devices, such as mobile phones, because they

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<sup>30</sup> James C. Salamanca, et al., *Formaldehyde Hemiacetal Sampling, Recovery, and Quantification from Electronic Cigarette Aerosols*, 7 *Sci. Reports* 11044 (2017).

<sup>31</sup> Jiries Meehan-Atrash, Wentai Luo & Robert M. Strongin, *Toxicant Formation in Dabbing: The Terpene Story*, 2 *ACS Omega* 6112 (Sept. 22, 2017).

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employ the same underlying battery cell technologies and manufacturing methods. Similar standards could be developed and implemented nationally for devices used to vaporize cannabis.

A third mode of cannabis inhalation called dabbing has also risen in popularity in recent years. In this mode of consumption, a significant amount of a cannabis extract (anywhere from milligrams to grams) is rapidly heated to very high temperatures in an apparatus called a dabbing rig (essentially a bong coupled to a strong heating element), which allows the user to rapidly inhale a very large dose of cannabis extract in one or two breaths. This form of cannabis use may be associated with safety concerns. For example, users often use very high cannabis doses (even in the gram range) that are very likely to produce effects due to interaction with protein receptors in addition to cannabinoid receptors, leading to off-target induced physiological changes. Some dabbers have reported symptoms—potent hallucinations, loss of balance, nausea, and vomiting—that are not typically associated with other forms of cannabis consumption. As described above, a second concern relates to the very high temperature used in dabbing, resulting in the formation of new molecules with established toxicities.

The consumption of cannabis-containing edible products is another common and growing form of cannabis consumption. In this case, an extract of cannabis oil is introduced into a food or beverage (e.g., into candies, chocolates, or cookies). The oral consumption of cannabis-containing products results in physiological responses that have a delayed onset (30-90 minutes) relative to inhaling cannabis and are more pronounced and longer-lasting than when cannabis is smoked or vaped. It is hypothesized that these effects may be due to the metabolism of (–)-*trans*- $\Delta^9$ -tetrahydrocannabinol (THC) to 11-OH- $\Delta^9$ -THC in the gut and liver. 11-OH- $\Delta^9$ -THC is hypothesized to cause a stronger high than THC, and the pharmacokinetics of cannabinoid accumulation is a gradual increase to very high levels over a long time rather than the fast spike in levels that occurs after inhalation. As with the inhalation of cannabis, the oral ingestion of cannabis does not present any major safety concerns (beyond the more intense physiological high connected to oral ingestion). Nonetheless, because some consumers, especially naïve consumers making their first purchase of a cannabis edible, are unaware of the strength of an edible, some states like California have instituted regulations that limit the dose of edibles (e.g., 10 mg max per ingested unit size, 100 mg max/package in California). These regulations allow consumers to carefully control the desired dose of cannabis they want.

A final mode of delivery of cannabis is through absorption, which occurs with transdermal patches, salves, and balms that contain cannabis or hemp oil. The pharmacokinetics of cannabinoid absorption into the bloodstream in topical products has not been well studied, but it is generally accepted that insignificant concentrations of THC, CBD and other cannabinoids accumulate in blood after the use of such products. Most of these products are intended to have a local effect, for example, on inflammation. To date, no significant safety issues have arisen with these products.

- **How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?**

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Unfortunately, only a limited number of scientific studies have formally addressed whether cannabis or cannabis-derived compounds interact with other substances.<sup>32</sup> It is known that THC and CBD are metabolized by a class of proteins that metabolize drugs in the liver, called cytochrome p450 enzymes, which could theoretically lead to potential drug-drug interactions. For example, CBD inhibits two of these drug-metabolizing enzymes, CYP3A4 and CYP2D6. As CYP3A4 metabolizes about a quarter of all drugs, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin). CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, antipsychotics, beta blockers, and opioids (including codeine and oxycodone). One recent case report described a drug-drug interaction between CBD and tacrolimus, an immunosuppressant drug used after organ transplants.<sup>33</sup> Another case study also found a drug-drug interaction between CBD and warfarin.<sup>34</sup> It is also well established that cannabis has additive central nervous system (CNS) depressant effects with alcohol, barbiturates, and benzodiazepines. Overall, given the widespread consumption of cannabis in society and relative absence of adverse events associated with cannabis use, one can infer that drug-drug interactions are unlikely to present a significant safety concern with cannabis or its components. Nonetheless, further research could address this question formally. Mechanisms to report potential drug-drug interactions should also be established.

Another possible safety concern relates to the effects of cannabis and its components on the endocannabinoid system. A wealth of data indicates that phytocannabinoids interact with numerous cannabinoid receptors, which are expressed on most cells, including neurons, and mediate numerous physiological reactions that are critically important in health and disease. How exactly cannabis and its components modulate the endocannabinoid system is not well understood. However, it is possible that daily exposure to CBD or other phytocannabinoids might influence normal physiological responses to drugs via an indirect effect on the endocannabinoid system. For example, if CBD has an anxiolytic (anti-anxiety) effect, which has been shown in one clinical study,<sup>35</sup> then one could infer that consumers who have anxiety and decide to take CBD might need to adjust their drug treatment regimen (for example, they might need to lower the dose they are taking of an SSRI). Nevertheless, these potential safety concerns are likely to be relevant only for consumers/patients taking high doses of CBD or other cannabinoids (for example, patients taking Epidiolex®). The doses of CBD that are ingested by

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<sup>32</sup> *Medical Cannabis: Adverse Effects & Drug Interactions*, Government of the District of Columbia Department of Health (Dec. 22, 2015), at 12-13, <https://dchealth.dc.gov/publication/medical-cannabis-adverse-effects-and-drug-interactions> (follow "Attachment(s)" hyperlink).

<sup>33</sup> Abbie D. Leino, et al., *Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus*, *Am. Journal of Transplantation* (Apr. 23, 2019), <https://onlinelibrary.wiley.com/doi/pdf/10.1111/ajt.15398>.

<sup>34</sup> Leslie Grayson, et al., *An interaction between warfarin and cannabidiol, a case report*, *Epilepsy & Behavior Case Reports*, 2018, at 10.

<sup>35</sup> Ila M. Linares, et al., *Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test*, 41 *Brazilian Journal of Psychiatry* 9 (2019).

the majority of consumers who purchase CBD products over the counter, in cannabis dispensaries, or online are in a much lower range (5-100 mg/dose) than the doses of Epidiolex® used to treat an illness (>1 g/day) and are unlikely to present any significant safety concerns due to drug-drug interactions.

**2. Are there special human populations (e.g. children, adolescents, pregnant or lactating women) or animal population (e.g. species, breed, or class) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds.**

There is scientific evidence that some human populations need to be considered carefully when assessing the safety of products containing cannabis and cannabis-derived compounds. Therapeutic regimes of cannabis and cannabis-derived compounds need to be approached carefully in medically fragile populations such as young children, seniors, and immunocompromised patients. There is compelling evidence from studies in animals that the endocannabinoid system influences brain development.<sup>36</sup> Therefore, because cannabis and cannabis-derived compounds interact with the endocannabinoid system, pregnant women, nursing women, children, and adolescents should consult their physician before being exposed to cannabis and its component molecules. THC exposure has been shown to impair brain development in young animals even at low doses,<sup>37</sup> so children, pregnant women, and nursing women using CBD products with trace amounts of THC (0.3% or less) should do so only under the supervision of a physician. Furthermore, patients with psychiatric diseases should also consider avoiding cannabis, given that cannabis use might exacerbate psychiatric symptoms in these patients.

**3. What are the characteristics of a successful system to collect representative safety information at the national or state level about products containing cannabis or cannabis-derived compounds?**

- **Are there systems that currently exist for the collection of this information (other than FDA's systems)?**

We believe that states that legalize medical and adult-use cannabis consumption should establish a successful system to collect representative safety information on cannabis products sold in those states. Oversight by state governmental regulatory bodies by using seed-to-sale inventory tracking systems has successfully identified cannabis products contaminated with pesticides and other contaminants, but we are unaware of any formal systems in place to report potential adverse events due to cannabis consumption. At the same time, it is important to emphasize that it is difficult to collect safety information at the state level on alcohol, cigarettes, or opiates, all of which have been scientifically proven to cause far more severe safety concerns than cannabis.

We believe that the best way to oversee potential safety issues with cannabis is to implement an effective and efficient regulatory program that monitors products in the market. Defining what

<sup>36</sup> Ila M. Linares, et al., *Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test*, 41 *Brazilian Journal of Psychiatry* 9 (2019).

<sup>37</sup> Patrícia Schonhofen, et al., *Cannabinoid-Based Therapies and Brain Development: Potential Harmful Effect of Early Modulation of the Endocannabinoid System*, 32 *CNS Drugs* 697 (Aug. 2018).

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information must be accessible on a product label and what claims can be made about a company's products is an important first step in protecting public health and safety, and in states that have legalized cannabis, laws have been passed to address such concerns. A system should provide guidelines for what additives are safe in end products and what agricultural practices are safe for ingested products. These guidelines should be similar to what are used in the nutraceutical and food additives industries. Consumers should be able to know where the products come from, where they were manufactured, and what additives are in those products.

- **Are there particular safety concerns related to the overlap of therapeutic dose levels from approved drug products, with potential exposure from other uses (e.g., from food, dietary supplements, cosmetics)? Please identify any safety concerns and include relevant data or studies.**

We are unaware of any safety concerns related to the overlap of therapeutic dose levels from approved drug products with potential exposure from other uses (e.g., from food, dietary supplements, or cosmetics).

**4. What end points or outcomes would define a maximal acceptable daily intake from all products?**

- **What margin of exposure would represent an appropriate and safe level from anticipated cumulative exposure? Does that margin of exposure vary based on the form of consumption (e.g., from ingestion, absorption, inhalation)? Please explain your reasoning and include relevant data or studies.**

It is difficult to define a maximal acceptable daily intake from cannabis products because levels and modes of consumption in the general population vary widely. For example, one consumer using cannabis for anxiety might ingest an edible product with 5 mg of THC once daily, while a patient with severe post-traumatic stress disorder (PTSD) might require 500 mg THC once daily to function normally. In the case of CBD, as stated above, numerous clinical studies have shown that CBD is safe and well tolerated in humans, even at very high (> 30 mg/kg/day) doses. This dose is approximately equivalent to 2,800 mg per day for the average adult male, 2,000 mg per day for the average adult female, and 550 mg per day for the average child. In humans, CBD exhibits no effects indicative of any abuse or dependence potential.<sup>38, 39, 40, 41</sup> To date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD.<sup>42</sup> In a large clinical study, the two most common side effects of high-dose

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<sup>38</sup> See *supra* note 14.

<sup>39</sup> See *supra* note 15.

<sup>40</sup> See *supra* note 16.

<sup>41</sup> See *supra* note 17.

<sup>42</sup> See *supra* note 18.

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CBD (25-50 mg/kg/day) were diarrhea and somnolence, which occurred in only a minority of subjects studied (24% and 30%, respectively).<sup>43</sup>

The vast majority of cannabis consumers are able to determine a maximal acceptable daily intake from cannabis products based on their own personal experience, given that scientific data supporting the establishment of a maximum safe level for cannabis is lacking except in the case of isolated CBD and THC, which we believe present no significant safety concerns even at high doses. As described in detail above, the margin of exposure for cannabis products does vary based on the form of consumption.

- **What mechanisms would be available to help ensure that this margin of exposure was maintained at a level sufficiently protective of public health?**

As stated above, studies to determine how the margin of exposure to cannabis products relates to public health are uncommon, and the few studies that exist suggest that there are no major safety concerns at any margin of exposure, except in certain individuals with severe psychiatric or immunocompromised conditions. States should consider instituting a formal system for reporting adverse events that may help further investigate whether high margins of exposure are correlated to an increase in adverse events.

Considering that most CBD products on the market are dosed in the 5-50 mg range, we have confidence, based on clinical research to date, that these products are very safe for public consumption. One might consider establishing regulations in which there is a bifurcation of CBD products: (1) FDA-approved drugs in the pharmaceutical market that are allowed to make health claims based on clinical research; and (2) cannabis products in the consumer market that do not and cannot make any health claims but are safe for public consumption because they are sold at lower doses already established by published clinical research to be safe.

More broadly speaking, it is clear that many individuals combine modern medicine and herbal remedies, including cannabis, to improve their health and even treat diseases. It is not uncommon to hear patients indicate that they beat cancer through changing their lifestyle and eating habits and by using supplements that helped mediate bouts with chemotherapy, as an example.

**5. Are there any data known that would support the safe use of cannabis and cannabis related compounds in general food use (including dietary supplements), including data regarding exposure levels to cannabis and cannabis-related compounds in foods (including dietary supplements) that would be acceptable from a food safety perspective?**

We are unaware of any formal scientific study that has investigated safety issues relating to consumption of cannabis-containing food products. As stated above, given the widespread consumption of cannabis in edible products and minimal amount of cannabis-induced adverse events reported in emergency rooms, the consumption of cannabis-containing food products does

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<sup>43</sup> Linda C. Laux, et al., *Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results*, Epilepsy Research, Aug. 2019, at 13.

not appear to present any significant safety concerns. The same is true for food products containing CBD.

- **What data are available about residues of cannabis-derived compounds in human foods (e.g., meat, milk, or eggs) that come from animals that consume cannabis or cannabis-derived compounds? Are there residue levels that should be tolerated in these foods? Please provide data or other information to support your reasoning.**

We are unaware of any scientific studies that attempted to determine whether cannabis-derived compounds are found in human foods that come from animals that consume cannabis or cannabis-derived compounds.

**6. How does the existing commercial availability of food products containing cannabis derived compounds such as CBD (which may in some cases be lawful at the state level but not the federal level) affect the incentives for, and the feasibility of, drug development programs involving such compounds?**

- **How would the incentives for, and the feasibility of, drug development be affected if food products containing cannabis-derived compounds, such as CBD, were to become widely commercially available?**

The widespread commercial availability of food products containing cannabis-derived compounds (such as CBD) has no significant effect on the incentives for, and feasibility of, drug development of compounds in the cannabinoid space. Strong evidence to support this argument is the fact that numerous cannabinoid-based medicines already exist in the pharmacopeia (e.g., Marinol® (dronabinol), Sativex® (nabiximols), Cesamet™ (nabilone), and Epidiolex®).

A completely novel way to trigger the beneficial pathways that cannabinoid receptors regulate is to target the enzymes that determine the fate of endocannabinoids themselves. A number of pharmaceutical companies (e.g., Pfizer, Johnson & Johnson, and Merck) are in clinical development to test inhibitors of an enzyme called fatty acid amide hydrolase (FAAH) for a wide variety of clinical indications, including social anxiety disorder, osteoarthritis pain, insomnia, and Tourette's.

With respect to CBD, it is important to emphasize that Epidiolex® is distinct from over-the-counter (OTC) products currently sold in consumer markets. Epidiolex® is a highly purified (>99% pure) form of CBD, essentially free from any other hemp-derived phytocompounds. The extraction and isolation of CBD and the exclusion of the other elements of the hemp plant provides a far different product than products derived from the whole hemp plant that contain naturally occurring CBD, which are becoming more and more commonplace in the nutraceutical and supplement markets.

The federal government should not be in the business of restricting the sale of cannabis-based products to enable a small number of pharmaceutical companies to profit greatly from the sale of cannabis-based drugs. If pharmaceutical companies choose to develop a cannabis-based drug, the FDA drug-approval process offers a viable and proven system to accomplish that goal

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successfully. In contrast, if consumers decide to purchase cannabis-based products through legal state-regulated dispensaries to successfully self-medicate, then they should not be restricted from doing so to protect the financial interests of the pharmaceutical industry. The two systems must remain mutually exclusive. The interest in and desire to pursue exploration of prescription drug benefits of isolated forms of phytocannabinoids like CBD will not be impeded by the products derived from the whole hemp plant operating in the non-drug product world. In fact, one of the most widely used medications in the world, aspirin, was originally derived from willow bark, and to this day, both aspirin and willow bark extract have found a niche in their respective medicinal and consumer worlds.

Notwithstanding the above, the FDA has already implemented a regime in addressing similar concerns, most notably in how it permits and regulates prescription and OTC versions and supplements of products with similar active pharmaceutical ingredients (APIs). Prescription medications like Lovaza and Vascepa, which treat high triglyceride levels with the intake of omega-3 fatty acids, have undergone the FDA's drug approval process. These products can contain up to 90% omega-3 fatty acids and are prescribed to manage and treat elevated triglyceride levels. Alternatively, fish oil supplements can contain anywhere between 30% and 50% of omega-3 fatty acids and are used in a similar daily wellness regime without prescription. The same alternative regimes with variations in dosage are a common feature of many products with both prescribed and OTC versions in other pharmacological arenas as well. OTC non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and acetaminophen are available in lower individual dose amounts than in their prescribed counterparts. The FDA could continue to use this dosing difference to promote and support drug development not only for CBD but for other novel phytocannabinoids found in the hemp and cannabis plants.

Despite the superficial similarities between prescription medications like Lovaza and Vascepa and their supplement counterparts, the differences are quite stark and provide support for a regime where FDA-approved drugs and supplements can coexist. First, insurance coverage for prescription medications can make drugs substantially cheaper for the consumer than a perceived OTC counterpart. This is especially true given the difference in individual dosages permitted under each regime. In many instances, supplement use is cost-prohibitive when compared to a prescribed counterpart.

Additionally, many of the hemp-derived non-drug consumer products are in forms as varied as foods, topicals, transdermals, lotions, and cosmetics and are therefore far different than the isolated cannabinoid products pursued by the pharmaceutical industry, and they have a number of different ingredients that could influence the pharmacology of CBD and other phytocannabinoids. Further, their application as a topical or cosmetic is, in many instances, significantly different than FDA-approved drug treatments that patients ingest.

In summary, the FDA has already implemented the infrastructure and qualifications that allow drugs and consumer products to coexist even when containing the same API. Differences in dose, route, or form of administration, purity of API, analogs, etc., allow certain compounds to coexist in the pharmaceutical and consumer markets. By simply applying these approaches to CBD, and possibly other isolated and purified phytocannabinoids, the pharmaceutical and hemp industries would maintain the ability to pursue their respective businesses.

- **How would this change if FDA established thresholds on acceptable levels of cannabinoids, including CBD, in the non-drug products it regulates? What else could FDA do to support drug development from cannabinoids?**

There is no strong scientific evidence to support the establishment of thresholds on acceptable levels of cannabinoids, including CBD, in the non-drug products the FDA regulates. However, if, for example, the FDA chose to establish such thresholds, we hope that it will follow the states' lead in terms of defining acceptable thresholds (e.g., limiting the maximum levels of THC in edible products, as occurs in California and Colorado). It is not the role of the FDA to facilitate drug development by the pharmaceutical industry; it is the FDA's role to oversee the drug approval process and to ensure the safety of food and other consumable products. If the federal government would like to support cannabinoid-based drug development, then it should deschedule cannabis and fund drug development studies through the National Institutes of Health funding programs.

## **Manufacturing and Product Quality**

1. **Are there particular standards needed to address any safety issues related to the manufacturing, processing, and holding of products containing cannabis and cannabis-derived compounds (e.g. genotoxic impurities, degradation of active compounds)? Please identify or describe those standards.**

A wide variety of products containing cannabis are on the market. CBD-infused foods, topicals, tinctures, oils, and dog treats are just a few examples. Most types of cannabis-infused products can be manufactured in a manner similar to the corresponding non-infused product. Experience gained from other industries (e.g., food, dietary supplement, and agriculture industries) should be used to create best practices and standards addressing the safety concerns in manufacturing, processing, and holding of cannabis products. Many of the standards that already exist or are in progress in the cannabis space are inspired by current Good Manufacturing Practice (cGMP) and safety plans in other industries. The same critical components of safety standards in other industries are needed in the manufacturing and processing of cannabis-infused products.

Like other industries, the major concern in the manufacturing, processing, and storing of cannabis-infused products is product, consumer, and employee safety. Currently, there is a patchwork of state laws governing safety tolerances. In some cases, these state laws call for testing for different contaminants based on requirements in similar industries rather than health risk assessments specific to cannabis and cannabis-derived products. For example, Colorado requires testing for 13 pesticides in marijuana,<sup>44</sup> whereas California requires testing for 66 pesticides,<sup>45</sup> some of which can exist in cannabis products as genotoxic impurities. Each state also has a different acceptable limit for pesticides, as demonstrated in Table 1 below. There are no established tolerances for hemp. Accordingly, consensus acceptance tolerances are needed to

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<sup>44</sup> 1 Colo. Code Regs. § 212-2 R 712.

<sup>45</sup> Cal. Code Regs. tit. 16, § 5719.

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address potential safety concerns such as pesticides, residual solvents, and microbial contaminants for hemp-derived CBD products.

Table 1. Comparison of Acceptable Limits for 13 Pesticides in California and Colorado

Pesticide	Acceptable Limit in ppb		
	California <sup>2</sup> (inhalable products)	California <sup>2</sup> (other products)	Colorado <sup>1</sup> (all products)
Abamectin	100	300	70
Azoxystrobin	100	40,000	20
Bifenazate	100	5,000	20
Etoxazole	100	1,500	10
Imazalil	100	100	40
Imidacloprid	5,000	3,000	20
Malathion	500	5,000	50
Myclobutanil	100	9,000	40
Permethrin	500	20,000	40
Spinosad	100	3,000	60
Spiromesifen	100	12,000	30
Spirotetramat	100	13,000	20
Tebuconazole	100	2,000	10

Employee safety is ensured through compliance with Occupational Safety and Health Administration (OSHA) requirements, including proper and frequent training, personal protective equipment, personal hygiene policies, good housekeeping, and clear hazard communication. Companies in this space should similarly abide by OSHA requirements and conduct frequent employee training in order to protect employees from injury and toxic substances involved in the cultivation of cannabis and downstream manufacturing of products.

In recent years, organizations that develop consensus standards (e.g., ASTM) have started to assemble committees of subject-matter experts to create science-based solutions to address safety and quality related to cannabis and cannabis-derived products. It is the hope of this coalition that these standard-setting bodies will continue their important work, through collaboration with the private sector. Of course, any standards developed through collaborative process can be referenced in future regulations.

***Recommendation #1: Require Laboratory Testing***

In many states that have authorized medical or adult-use cannabis, independent, third-party laboratory testing of products is required to protect public health and address safety concerns. The third-party cannabis testing facilities are audited and certified by state regulators, and many are required to be accredited to the International Organization for Standardization and the International Electrotechnical Commission (ISO/IEC) 17025 standard. ISO/IEC 17025 specifies

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the requirements for the competence of testing and calibration laboratories for consistent and quality-based operation.<sup>46</sup> It is recommended that cannabis-derived products be tested to ensure safety. Laboratory testing of cannabis-derived products could be performed in-house as well as through third-party labs in a manner similar to the way it is done in other industries that must comply with cGMP requirements. The federal government could require such testing at the state level.

***Recommendation #2: Require cGMP Compliance and Implementation of Risk-based Approaches***

Equivalent third-party evaluations to determine laboratory adherence with ISO 17025 are already occurring in cannabis manufacturing facilities, such as cGMP certification and ISO 9001 accreditation. Companies providing cGMP audits and resources for cannabis manufacturing and processing facilities include Americans for Safe Access,<sup>47</sup> Foundation of Cannabis United Standards (FOCUS),<sup>48</sup> International Solutions,<sup>49</sup> ASI,<sup>50</sup> and Orion GMP Solutions.<sup>51</sup>

By using GMP and risk-based approaches from other industries, such as Environmental Monitoring Programs, Hazard Analysis and Critical Control Points (HACCP), and Preventive Controls, cannabis manufacturers can identify the critical points in their process that should be monitored to prevent product contamination with a toxic substance or degradation. For instance, providing personal hygiene policies, using cleaning and sanitization standard operating procedures (SOPs), and guaranteeing the facility is fit for purpose all help protect the health and safety of employees and consumers. It is recommended that cannabis product manufacturers comply with cGMP, either newly created cGMP specific to cannabis or cGMP from the corresponding industry (e.g., cannabis-infused foods manufactured according to C.F.R. Title 21, Part 117).

***Recommendation #3: Evaluate Proper Storage Conditions***

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<sup>46</sup> International Organization for Standardization [ISO], *General requirements for the competence of testing and calibration laboratories*, ISO/IEC 17025:2017 (3d ed. Mar. 2018), <https://www.iso.org/home/standards/popular-standards/isoiec-17025-testing-and-calibra.html>.

<sup>47</sup> *Patient Focused Certification*, Americans for Safe Access Foundation, <https://safeaccess2.org/patientfocusedcertification/> (last visited May 21, 2019).

<sup>48</sup> *FOCUS Certification*, Foundation Of Cannabis United Standards, <https://www.focusstandards.org/cannabis-certification/> (last visited May 21, 2019).

<sup>49</sup> *GMP for Medical Cannabis Industry?*, International Certifications, <https://intlcert.com/gmp-for-cannabis/> (last visited May 21, 2019).

<sup>50</sup> *Cannabis Safety and Quality*, ASI, <https://asifood.com/cannabis/> (last visited May 21, 2019).

<sup>51</sup> *Quality Pharmaceuticals and Process by Design*, Orion GMP Solutions, <http://oriongmp.com/> (last visited May 21, 2019).

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Controlling and monitoring aspects of cannabis cultivation, manufacturing, and storage facilities, such as light,<sup>52</sup> temperature,<sup>53</sup> and humidity,<sup>54</sup> and limiting storage time have been shown to prevent degradation of active cannabinoids in cannabis products, avoiding mislabeling issues. Stability testing of products under different conditions can be used to evaluate the proper storage conditions. These studies are important because products with acidic cannabinoids, known to be “inactive,” can decarboxylate into their active forms with exposure to light and/or heat. Further, active, decarboxylated cannabinoids can further degrade into other cannabinoids. For instance, THC degrades over time mainly to cannabinoids cannabidiol (CBD).

There are limited studies examining the stability and degradation of cannabinoids in different products. Lindholst investigated the stability of cannabinoids in cannabis resin slabs and extracts over four years. He found that acidic tetrahydrocannabinol (THC-A) decarboxylates into THC exponentially with half-lives of 330 and 462 days in light and darkness, respectively. The degradation of THC was shown to be slower. However, THC-A converted to THC faster in cannabis extracts, with half-lives of 35 and 91 days in light and darkness.<sup>55</sup> This study indicates that the degradation of cannabinoids in various products may be different and need to be evaluated for proper labeling of cannabinoid concentration and expiration dates. It is recommended that manufacturers evaluate the proper storage conditions and perform stability testing of their products.

***Recommendation #4: Use Consensus Standards as References***

Consensus standards from organizations such as ISO, ASTM International, American National Standards Institute (ANSI), and the U.S. Pharmacopeial Convention (USP) have been referenced in regulations and provided as resources for congruent industries. Some of these organizations are forming committees specifically to develop standards for cannabis and its manufacturing processes.

An organization that is gaining steam on this mission is ASTM, formerly known as American Society for Testing and Materials. In 2017, ASTM formed Committee D37 on Cannabis to develop standards for cannabis and its products and processes. The ASTM Committee D37 consists of eight subcommittees: Indoor and Outdoor Horticulture and Agriculture, Quality Management Systems, Laboratory, Processing and Handling, Security and Transportation, Personnel Training/Assessment/Credentialing, Industrial Hemp, and Terminology.<sup>56</sup>

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<sup>52</sup> Irenne Gabriela Trofin, et al., *Long-term storage and cannabis oil stability*, 53 *Revista de Chimie* (Bucharest) 294 (March 2012).

<sup>53</sup> Mei Wang, et al., *Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry*, 1 *Cannabis and Cannabinoid Research* 262 (2016).

<sup>54</sup> *How to Control Humidity When Storing Your Cannabis*, Leafly, <https://www.leafly.com/news/cannabis-101/controlling-humidity-when-storing-cannabis> (last visited May 21, 2019).

<sup>55</sup> Christian Lindholst, *Long term stability of cannabis resin and cannabis extracts*, 42 *Australian Journal of Forensic Sciences* 181 (2010).

<sup>56</sup> *Committee D37 on Cannabis*, ASTM International, <https://www.astm.org/COMMITTEE/D37.htm> (last visited May 21, 2019).

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The ASTM Committee D37 has published standards specifically for cannabis that address safety issues related to manufacturing, processing, and holding of products. D8219-19, the Standard Guide for Cleaning and Disinfection at a Cannabis Cultivation Center, presents information on techniques and products used for cleaning, disinfection, and mitigation of hazards. Using this guide, cleaning and disinfection can be incorporated into integrated pest management programs, as scheduled maintenance, for specific events, or at critical control points.<sup>57</sup> D8250-19, the Standard Practice for Applying a HACCP System for Cannabis Consumable Products, is a practice that provides general guidelines for the development and implementation of a HACCP system for operations that manufacture cannabis consumable products to prevent, control, or minimize hazards (biological, chemical, or physical) to an acceptable level.<sup>58</sup> A HACCP system can prevent consumer harm when implemented and followed correctly.

The ASTM Committee D37 is currently working on other standards that address safety issues and pull from cGMP in other industries. Examples include:

- WK64711, Specification for Sanitation and Cleaning. This specification will focus on sanitation and cleaning for indoor and outdoor cultivation and agriculture operations to ensure that no biological contamination occurs and employees have working environments that provide a safe and sanitary area to work and operate.<sup>59</sup>
- WK60435, Specifications for Solvent Based Cannabis Extraction Equipment. This specification will develop standard construction and safety specifications for solvent-based cannabis extraction equipment to maintain safe operation.<sup>60</sup>
- WK65011, Training and Certification for Multiple Roles and Vocations Within the Cannabis Industry. This guide will provide a foundation for an ASTM-based training program for various functions within the cannabis industry.<sup>61</sup>
- WK67891, Minimum Food Safety and Quality of Whole Nutritional Cannabis (Hemp) Seed/Grain Intended for Human/Animal Consumption. This standard will define the minimum international food safety and quality specifications for whole nutritional cannabis (hemp) seed/grain intended for human and animal consumption.<sup>62</sup>

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<sup>57</sup> Subcommittee D37.01, *Standard Guide for Cleanings and Disinfecting at a Cannabis Cultivation Center*, ASTM D8219-19 (2019), <https://www.astm.org/Standards/D8219.htm>.

<sup>58</sup> Subcommittee D37.02, *Standard Practice for Applying a Hazard Analysis Critical Control Points (HACCP) System for Cannabis Consumable Products*, ASTM D8250-19 (2019), <https://www.astm.org/Standards/D8250.htm>.

<sup>59</sup> Subcommittee D37.01, *New Specification for Specification for Sanitation and Cleaning*, ASTM WK64711 (Aug. 9, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK64711.htm>.

<sup>60</sup> Subcommittee D37.04, *New Specification for Specifications for Solvent Based Cannabis Extraction Equipment*, ASTM WK60435 (Sept. 6, 2017), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK60435.htm>.

<sup>61</sup> Subcommittee D37.06, *New Guide for Training and Certification for Multiple Roles and Vocations Within the Cannabis Industry*, ASTM WK65011 (Sept. 4, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65011.htm>.

<sup>62</sup> Subcommittee D37.07, *New Specification for Minimum Food Safety and Quality of Whole Nutritional Cannabis (Hemp) Seed/Grain Intended for Human/Animal Consumption*, ASTM WK67891 (April 17, 2019), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK67891.htm>.

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Other groups have also formed cannabis-focused committees to develop quality standards for the cannabis industry, such as USP's Expert Panel on Medical Cannabis<sup>63</sup> and AOAC International's Cannabis Analytical Science Program (CASP).<sup>64</sup>

***Recommendation #5: Provide and Enforce OSHA Safety Policies***

The manufacturing and processing of cannabis products have inherent hazard risks. For example, pesticide exposure is an employee risk in cultivation of cannabis. Machine hazards and flammable solvents pose risks in cannabis extraction facilities, like those in other botanical processing facilities.

Existing OSHA safety and health standards can provide adoptable requirements that can be enforced in the cannabis industry. In addition to OSHA's resources, the Colorado Department of Public Health & Environmental published a Guide to Worker Safety and Health in the Marijuana Industry to assist employers in building occupational safety and health programs.<sup>65</sup> It is recommended that cannabis manufacturing facilities be held to OSHA requirements and that more safety resources be made available that are specific to cannabis operations.

**2. Are there particular standards or processes needed to ensure manufacturing quality and consistency of products containing cannabis or cannabis-derived compounds, including standards applied to evaluate product quality? Please identify or describe those standards.**

The growing number of states legalizing cannabis has driven a focus on ensuring quality control and consistency of cannabis products. To ensure manufacturing quality, practices similar to those in the food, dietary supplement, cosmetics, agricultural, and pharmaceutical industries are necessary. Having harmonized regulations, requiring laboratory testing of products, establishing standardized test methods, gaining more access to reference materials, and mandating cGMP and other quality-based approaches for manufacturing processes are necessary to maintain product quality and consistency.

***Recommendation #1: Harmonize Regulations***

States with regulated cannabis markets have implemented several regulations that support the quality and consistency of cannabis products, but they differ from state to state. Such regulations cover issues including the types of testing performed, the testing methodologies used, and acceptable contamination limits. It is important to develop regulations to validate and verify that cultivation and manufacturing processes can produce consistent, safe products. Having varied requirements between states has caused confusion and made following regulations more difficult. In the interest of quality and safety, shared regulations to evaluate the quality of products would be beneficial and are highly recommended.

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<sup>63</sup> USP Expert Panel on Medical Cannabis, USP-NF (Aug. 30, 2016), <https://www.uspnf.com/notices/usp-expert-panel-medical-cannabis>.

<sup>64</sup> Cannabis Analytical Science Program, AOAC International, [https://www.aoac.org/AOAC\\_Prod\\_Imis/AOAC/SD/CASP/CASPAbout/AOAC\\_Member/SDCF/CASP/CASP\\_Main.aspx](https://www.aoac.org/AOAC_Prod_Imis/AOAC/SD/CASP/CASPAbout/AOAC_Member/SDCF/CASP/CASP_Main.aspx) (last visited May 21, 2019).

<sup>65</sup> Marijuana Occupational Health and Safety Work Group, *Guide to Worker Safety and Health in the Marijuana Industry*, Colorado Department of Public Health & Environment (Jan. 2017), <http://marijuanaindustrygroup.org/wp-content/uploads/2017/02/Guide-to-Worker-Safety-and-Health-in-the-Marijuana-Industry-FULL-REPORT-1.pdf>.

***Recommendation #2: Standardize and Require Laboratory Testing***

Testing samples of in-process and finished products helps ensure that they are fit for human consumption and are labeled with accurate ingredient information. Standardization of the testing that is performed is necessary to ensure that test results are reproducible and valid.

While states have different testing requirements, many states are testing for cannabinoid and terpene concentrations, foreign material, microbiological contaminants, pesticides, heavy metals, mycotoxins, and residual solvents. The tolerance levels for contaminants and permissible variance in label claims generally have lower acceptance limits than what is acceptable for equivalent industries, likely due to limited available safety data and novel modes of consumption. Further research is necessary to provide data-based tolerance levels in cannabis products.

Standardizing laboratory requirements should be required, including proper validation of methods (to prove that methods are robust and fit for purpose) and running frequent quality control checks to ensure that instrumentation and methods are in control. In addition, proficiency testing and interlaboratory comparisons are necessary to examine the competence of a testing program. Proficiency testing and interlaboratory comparisons have been difficult in the cannabis industry because of the federal illegality of transporting cannabis across state lines. Since passage of the 2018 Farm Bill, it has become somewhat easier to create proficiency test samples with hemp material, although there are still some states that treat hemp as a controlled substance. However, it would be useful to have the same access to other types of cannabis plants for proficiency testing. All these quality assurance and quality control practices are necessary to ensure manufacturing quality and consistency of cannabis products. Standardization of these practices across states is of great importance.

Standards of competence such as ISO 17025 are important in an industry that lacks an operational track record verifying the safety and quality of its products. Multiple third-party accreditation bodies openly work with cannabis testing laboratories to provide accreditation to international standards like ISO/IEC 17025, such as the American Association for Laboratory Accreditation (A2LA),<sup>66</sup> ANSI-ASQ National Accreditation Board (ANAB),<sup>67</sup> Perry Johnson Laboratory Accreditation (PJLA),<sup>68</sup> and the International Accreditation Service (IAS).<sup>69</sup> To date, there are at least 70 ISO 17025 accredited laboratories that test cannabis products with validated methods across 18 states listed on the websites of these four accreditation bodies. It is recommended that cannabis testing labs continue to be required to achieve ISO 17025 accreditation.

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<sup>66</sup> *Cannabis testing laboratory accreditation program*, A2LA, <https://www.a2la.org/accreditation/cannabis-testing> (last visited May 21, 2019).

<sup>67</sup> *Cannabis testing lab accreditation program*, ANSI National Accreditation Board, <https://www.anab.org/lab-related-accreditation/cannabis-testing> (last visited May 21, 2019).

<sup>68</sup> *Medical Marijuana Testing*, Perry Johnson Laboratory Accreditation, Inc., <http://www.pjlabs.com/accreditation-programs/medical-marijuana-testing> (last visited May 21, 2019).

<sup>69</sup> *Cannabis Testing Laboratory Accreditation*, International Accreditation Service, <https://www.iasonline.org/services/cannabis-testing-laboratory/> (last visited May 21, 2019).

***Recommendation #3: Standardize Cannabis Testing Using Reference Methods***

Standard test methods specific to cannabis and cannabis products are just now starting to be developed by consensus organizations. The general absence of reference test methods has forced cannabis laboratories to use their own in-house produced methods, which can vary greatly from lab to lab.

The range of concentrations and lowest concentration that can be detected are important parameters of a test method. Several “no tolerance” limits of contaminants have been based on the lowest concentration of the contaminant that a laboratory’s method can detect. Without reference methods to provide standardized specifications of detection limits and instrumentation across all labs, some labs may use more sensitive equipment and be able to detect lower concentrations than other labs. This means that one lab’s instrumentation and methodology may be able to detect a very minute amount of a prohibited pesticide, causing the product to fail compliance testing, while another lab’s does not.

Without reference test methods, results may not be reliable or reproducible. Many groups are working to bring greater consistency to cannabis testing, such as ASTM International,<sup>70</sup> AOAC International,<sup>71</sup> and other organizations. They are creating standardized reference test methods specifically to evaluate cannabis products.

***Recommendation #4: Make Quality Reference Materials More Accessible***

Reference materials are critical in validating analytical methods and assessing the reproducibility of test results among different labs and over time. The International Union of Pure and Applied Chemistry defines reference materials as a “material or substance one of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to materials” in the Compendium of Analytical Nomenclature.<sup>72</sup> Further, certified reference materials are those that are accompanied by a certificate and are certified by a procedure that establishes its traceability to a stated level of confidence.

One of the main challenges for laboratories is obtaining quality and concentrated reference materials for cannabinoid standards because they are considered by the U.S. Drug Enforcement Administration to be Schedule I drugs under the Controlled Substances Act. Reference standards are used to validate methods and challenge assay performance. They can also be traceable in case of downstream issues warranting investigations. The only standards available are for the

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<sup>70</sup> See *supra* note 53.

<sup>71</sup> See *supra* note 61.

<sup>72</sup> János Inczédy, Tamás Lengyel & Allan M. Ure, *Compendium of Analytical Nomenclature: Definitive Rules*, International Union of Pure and Applied Chemistry (3d. ed. 1997), [https://media.iupac.org/publications/analytical\\_compendium/](https://media.iupac.org/publications/analytical_compendium/) (last updated July 31, 2002).

major cannabinoids and they are at concentrations of  $\leq 1\text{mg/mL}$ ,<sup>73, 74, 75, 76</sup> This has caused some laboratories to create their own standards to provide better cannabinoid profiling, which can be costly and ineffective. Cannabis schedule change, or at least a carveout for reference materials, is required to enable access to higher quality and readily available reference materials.

***Recommendation #5: Require cGMP Compliance and Implementation of Risk-based Approaches***

It is recommended that cGMP compliance and risk-based programs such as HACCP and Preventive Controls be mandated to align the cannabis industry with other U.S. industries. In other industries, much of this has been accomplished by cGMP specific to a given industry. cGMP guidance is needed in the cannabis industry to maintain quality operations including effective quality management, risk-based preventive controls, monitoring programs, corrective actions, SOPs, recordkeeping, and employee cleanliness and hygienic practices.

***Recommendation #6: Use Consensus Standards as References***

It is recommended that consensus standards detailing quality practices for the cannabis industry be considered when creating regulations to ensure cannabis product consistency and quality. While several standards organizations are working on quality standards, an example of standards being developed by the ASTM Committee D37 include:

- WK62845, New Practice for Standard Operating Procedures and Records for a Cannabis Quality System. This practice will outline key aspects for successful management of SOPs and records. The effective development, control, and management of procedures and records is a fundamental building block for a robust, effective cannabis quality management system. A systematic approach should be implemented to provide a high level of assurance that all quality procedures, records, and data are complete and reliable throughout the cannabis supply chain.<sup>77</sup>
- WK60084, New Practice for Quality Management System (QMS) on Corrective Action Preventive Action (CAPA) for Cannabis Cultivation, Processing, Manufacturing, Testing, and Distribution. This practice will define the role of the CAPA system and the

<sup>73</sup> *Cannabinoids Standard*, Restek, <https://www.restek.com/catalog/view/11258/34014> (last visited May 21, 2019).

<sup>74</sup> *Analytical Reference Standards Catalog: Cannabinoids*, Cerilliant Analytical Reference Standards, [https://www.cerilliant.com/shoponline/product\\_cat\\_list.aspx?prodcat=42](https://www.cerilliant.com/shoponline/product_cat_list.aspx?prodcat=42) (last visited May 21, 2019).

<sup>75</sup> *Cannabinoid Standards*, Sigma-Aldrich, <https://www.sigmaaldrich.com/technical-documents/articles/analytical/cannabinoid-standards.html> (last visited May 21, 2019).

<sup>76</sup> *Analytical Cannabis Standards*, CPI International, <https://www.cpiinternational.com/analytical-cannabis-standards.html> (last visited May 21, 2019).

<sup>77</sup> Subcommittee D37.02, *New Practice for Practice for Standard Operating Procedures and Records for a Cannabis Quality System*, ASTM WK62845 (Mar. 23, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK62845.htm>.

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significance of an effective CAPA system within the QMS.<sup>78</sup>

- WK61355, Establishing an Effective Quality Management System (QMS) in the Cannabis Industry. This guide will establish a set of generally agreed-upon guidelines for an effective QMS framework for an organization that needs to demonstrate its ability to provide cannabis-related products or services that consistently meet consumer safety and applicable local and state regulatory requirements throughout the supply chain.<sup>79</sup>
- WK66055, New Practice for Cannabis Stability Plans. The purpose of this guide is to provide a template for creating stability plans for cannabis products. This includes determining when a cannabis product should be placed on stability, and the parameters of the stability plan, including test methods, timepoints, and storage conditions.<sup>80</sup>
- WK64674, New Guide for Implementing and Managing Hazard Analyses Critical Control Points (HACCP) Systems for extracted and infused products within the Cannabis Industry. This standard guide addresses the principles to follow when developing HACCP Systems for Cannabis extraction and infused product processes.<sup>81</sup>
- WK66158, New Guide for Food Safety Systems for Agricultural Cannabis Operations. This standard guide addresses the Good Agricultural Practices and Food Safety Controls needed to prevent food hazards in cannabis products that are grown for distribution to extraction facilities and dispensaries.<sup>82</sup>
- WK67088, New Practice for Cannabis Operation Compliance Audits. This standard provides guidelines for establishing and conducting periodic internal audits for a cannabis business to reliably provide quality and safe products.<sup>83</sup>
- WK67367, New Guide for Auditing and Self Inspection in the Cannabis Industry. This standard guide provides the minimum requirements for the conduct of compliance audits or self-inspections in the cannabis industry. The intended use of this standard guide is to provide a basis for an internal or external entity to develop and conduct an audit program

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<sup>78</sup> Subcommittee D37.02, *New Practice for Quality Management System (QMS) on Corrective Action Preventive Action (CAPA) for Cannabis Cultivation, Processing, Manufacturing, Testing, and Distribution*, ASTM WK60084 (Aug. 7, 2017), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK60084.htm>.

<sup>79</sup> Subcommittee D37.02, *New Guide for Establishing an Effective Quality Management System (QMS) in the Cannabis Industry*, ASTM WK61355 (Dec. 5, 2017), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK61355.htm>.

<sup>80</sup> Subcommittee D37.03, *New Practice for Cannabis Stability Plans*, ASTM WK66055 (Dec. 2, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK66055.htm>.

<sup>81</sup> Subcommittee D37.02, *New Guide for Implementing and Managing Hazard Analyses Critical Control Points (HACCP) Systems for extracted and infused products within the Cannabis industry*, ASTM WK64674 (Aug. 8, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK64674.htm>.

<sup>82</sup> Subcommittee D37.02, *New Guide for Food Safety Systems for Agricultural Cannabis Operations*, ASTM WK66158 (Dec. 7, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK66158.htm>.

<sup>83</sup> Subcommittee D37.02, *New Practice for Cannabis Operation Compliance Audits*, ASTM WK67088 (Feb. 12, 2019), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK67088.htm>.

focused on the cannabis industry.<sup>84</sup>

### 3. What validated analytical testing is needed to support the manufacturing of safe and consistent products?

Validated analytical testing is needed to ensure that cannabis products are safe, consistent, and free from harmful contaminants. To protect consumers from potentially hazardous microbes and dangerous chemical residues, each state with a cannabis testing program requires testing for various types of harmful contaminants. Cannabis, like any other type of consumer product, cannot feasibly be tested for every single potentially hazardous compound. Instead, contaminant testing must be targeted to the most likely forms of contamination that pose the greatest potential health hazards. Risk-based assessments are needed to identify specific lists of contaminants that should be screened and at what concentrations.

It is recommended that the cannabis industry perform testing that is appropriate to the type of product being produced and specific risks and hazards associated with that type of product. HACCP, Hazard Analysis and Risk-Based Preventive Controls (HARPC), and other risk-based approaches are recommended to identify the risks and necessary tests from business to business. To support the manufacturing of safe and consistent products, four categories of testing should be considered:

1. Microbial Contaminants: fungus (e.g., Total Yeast and Mold Count, *Aspergillus*, *Candida*), bacteria (e.g., Total Coliform Count, Total Enterobacteria Count, shiga-toxin producing *E. coli*, *Salmonella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*), mycotoxins (e.g., Ochratoxin A, Aflatoxins B1, B2, G1, G2).
2. Chemical Contaminants: residual solvents (class I, class II), pesticides (fungicides, insecticides, herbicides), heavy metals (e.g., lead, arsenic, cadmium, mercury).
3. Identity and Composition Testing: cannabinoids (e.g.,  $\Delta^9$ -THC, THC-A, CBD, CBD-A, CBG, CBG-A, CBN, CBC, CBC-A, THCV, THCV-A,  $\Delta^8$ -THC), terpenes (e.g., myrcene, caryophyllene, humulene, linalool, limonene, pinene, terpinene, terpinolene), nutritional composition for infused foods.
4. Stability and Shelf Life Testing: e.g., moisture content, water activity, rancidity, degradation of cannabinoids and terpenes, organoleptic testing of color, texture, aroma, and taste.

Validated test methods are limited in the cannabis space at this time. The ASTM Committee D37 is currently working on analytical testing standard methods and standards associated with laboratory testing, including:

- WK60319, Laboratory Test Method Validation and Method Development. This standard is needed to create a recognized harmonious standard for cannabis testing laboratories to

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<sup>84</sup> Subcommittee D37.02, *New Guide for Auditing and Self Inspection in the Cannabis Industry*, ASTM WK67367 (March 6, 2019), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK67367.htm>.

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adopt in the employment of robust validated methods.<sup>85</sup>

- WK64333, Multiresidue Analysis of Pesticides in Cannabis Leaves and Oils using Gas Chromatography-Mass Spectroscopy (GC-MS). This test method allows for the determination and concentration of pesticides in cannabis-containing oil using GC-MS.<sup>86</sup>
- WK64335, Multiresidue Analysis of Pesticides in Cannabis Leaves, Flowers, and Oil using HPLC-tandem mass spectroscopy (HPLC-MS/MS). This test method allows for the determination and concentration of pesticides in cannabis-containing leaves, flowers, and oils by HPLC-MS/MS.<sup>87</sup>
- WK65013, Determination of Cannabinoid Concentration in Cannabis Using High Performance Liquid Chromatography. This test method provides a validated procedure for determining five critical cannabinoid concentrations in fresh, dried, and derived products of cannabis and hemp by HPLC.<sup>88</sup>
- WK65014, Analyses of Terpenes in Cannabis using Gas Chromatography-tandem Mass Spectrometry (GC-MS/MS). This test method provides a validated procedure for analyzing a series of common terpenes in cannabis by GC-MS/MS.<sup>89</sup>
- WK65015, Analyses of Trace Elements in Cannabis by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). This method provides procedures for determination of total recoverable element concentrations (including heavy metals) in cannabis plant tissues and oils by ICP-MS.<sup>90</sup>
- WK65018, Analysis of Class 2 Residual Solvents in Cannabis Oil. This test method provides a validated procedure for analyzing for the presence of Class 2 and some Class 3 residual solvents in cannabis products by HS-GC-MS.<sup>91</sup>
- WK65194, Stability Testing Standard Guide for Cannabis Products. This standard will

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<sup>85</sup> Subcommittee D37.03, *New Practice for Laboratory Test Method Validation and Method Development*, ASTM WK60319 (Aug. 28, 2017), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK60319.htm>.

<sup>86</sup> Subcommittee D37.03, *New Test Method for Multiresidue Analysis of Pesticides in Cannabis Leaves and Oils Using Gas Chromatography-Mass Spectroscopy (GC-MS) 1*, ASTM WK64333 (July 12, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK64333.htm>.

<sup>87</sup> Subcommittee D37.03, *New Test Method for Multiresidue Analysis of Pesticides in Cannabis Leaves, Flowers, and Oil using HPLC-tandem mass spectroscopy (HPLC-MS/MS)*, ASTM WK64335 (July 12, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK64335.htm>.

<sup>88</sup> Subcommittee D37.03, *New Test Method for Determination of Cannabinoid Concentration in Cannabis Using High Performance Liquid Chromatography*, ASTM WK65013 (Sept. 4, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65013.htm>.

<sup>89</sup> Subcommittee D37.03, *New Test Method for Analyses of Terpenes in Cannabis Using Gas Chromatography-tandem Mass Spectrometry (GC-MS/MS)*, ASTM WK65014 (Sept. 4, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65014.htm>.

<sup>90</sup> Subcommittee D37.03, *New Test Method for Analyses of Trace Elements in Cannabis by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)*, ASTM WK65015 (Sept. 4, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65015.htm>.

<sup>91</sup> Subcommittee D37.03, *New Test Method for Analysis of Class 2 Residual Solvents in Cannabis Oil*, ASTM WK65018 (Sept. 4, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65018.htm>.

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provide information on the stability of the cannabis plant after harvesting and processing and how it relates to the shelf-life of products.<sup>92</sup>

- WK65402, Determination of Cannabinoids in thermally prepared food products (edibles) using Thermal desorption Gas chromatography/mass spectrometry (TD-GC/MS) or Gas chromatography flame ionization detector (GC/FID). This test method provides a procedure to identify and quantify cannabinoids in a broad range of edible products.<sup>93</sup>
- WK67498, Determination of Cannabinoid Concentration in Cannabis Using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). This test method details the analytical procedure for the analysis of cannabis to determine the identity and concentration of individual cannabinoids using LC-MS/MS.<sup>94</sup>

AOAC CASP has published Standard Method Performance Requirements (SMPRs®) for the Identification and Quantitation of Selected Pesticide Residues in Dried Cannabis Materials, the Quantitation of Cannabinoids in Dried Plant Materials, and the Quantitation of Cannabinoids in Cannabis Concentrates.<sup>95, 96, 97</sup> CASP has recently formed three working groups to develop SMPRs and/or Official Methods of Analysis for chemical contaminants, microbial contaminants, and cannabinoids in cannabis and hemp consumables.

Individual research groups have also published analytical testing methods in peer-reviewed journals for the identification and quantification of cannabinoids in different products. Examples of this published research include Meng et al. (2018), Gul et al. (2015), Brighenti et al. (2017),

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<sup>92</sup> Subcommittee D37.03, *New Guide for Stability Testing Standard Guide for Cannabis Products*, ASTM WK65194, <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65194.htm>.

<sup>93</sup> Subcommittee D37.03, *New Test Method for Determination of Cannabinoids in thermally prepared food products (edibles) using Thermal desorption Gas chromatography/mass spectrometry (TD-GC/MS) or Gas chromatography flame ionization detector (GC/FID)*, ASTM WK65402 (Oct. 16, 2018), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK65402.htm>.

<sup>94</sup> Subcommittee D37.03, *New Test Method for Determination of Cannabinoid Concentration in Cannabis Using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)*, ASTM WK67498 (Mar. 18, 2019), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK67498.htm>.

<sup>95</sup> AOAC International, *Identification and Quantitation of Selected Pesticide Residues in Dried Cannabis Materials*, AOAC SMPR 2018.011 (Aug. 26, 2018), [http://www.aoc.org/AOAC\\_Prod\\_Imis/AOAC\\_Docs/SMPRs/SMPR2018\\_011.pdf](http://www.aoc.org/AOAC_Prod_Imis/AOAC_Docs/SMPRs/SMPR2018_011.pdf).

<sup>96</sup> AOAC International, *Quantitation of Cannabinoids in Dried Plant Materials*, AOAC SMPR 2017.002 (Mar. 13, 2017), [http://www.aoc.org/AOAC\\_Prod\\_Imis/AOAC\\_Docs/SMPRs/SMPR%202017\\_002.pdf](http://www.aoc.org/AOAC_Prod_Imis/AOAC_Docs/SMPRs/SMPR%202017_002.pdf).

<sup>97</sup> AOAC International, *Quantitation of Cannabinoids in Cannabis Concentrates*, AOAC SMPR 2017.001 (Mar. 13, 2017), [http://www.aoc.org/AOAC\\_Prod\\_Imis/AOAC\\_Docs/SMPRs/SMPR%202017\\_001.pdf](http://www.aoc.org/AOAC_Prod_Imis/AOAC_Docs/SMPRs/SMPR%202017_001.pdf).

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and Mudge et al. (2017).<sup>98, 99, 100, 101</sup>

Analytical instrumentation manufacturers have published white papers and analytical application notes on testing methods specific to cannabis and cannabis products. SCIEX, Agilent, Restek, PerkinElmer, Phenomenex, and others cater to the industry and have all released application notes detailing analytical methods that can be used for cannabis testing.<sup>102, 103, 104, 105, 106</sup>

It is recommended that validated analytical test methods be used to quantify cannabinoids and terpenes and detect contaminants in cannabis products. Reference test methods from consensus standard organizations, peer-reviewed published methods, and application notes from instrument manufacturers can be used to support the manufacturing of safe and consistent products.

**4. Are there any currently used standardized definitions for the ingredients in cannabis products (eg: hemp oil)? If standardized definitions would be helpful, what terms should be defined and what should the definitions be?**

Standardized definitions are necessary for cannabis products. For example, the words cannabis, marijuana, and hemp are often used interchangeably, causing confusion among manufacturers and consumers. There are several examples of definitions for cannabis products and associated ingredients; however, these vary from state to state. It is important to harmonize definitions nationally.

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<sup>98</sup> Qingfang Meng, et al., *A reliable and validated LC-MS/MS method for the simultaneous quantification of 4 cannabinoids in 40 consumer products*, 13 PLOS One e0196396 (May 2, 2018).

<sup>99</sup> Waseem Gul, et al., *Determination of 11 Cannabinoids in Biomass and Extracts of Different Varieties of Cannabis Using High-Performance Liquid Chromatography*, 98 Journal of AOAC International 1523 (2015).

<sup>100</sup> Virginia Brighenti, et al., *Development of a new extraction technique and HPLC method for the analysis of non-psychoactive cannabinoids in fibre-type Cannabis sativa L. (hemp)*, 143 Journal of Pharmaceutical and Biomedical Analysis 228 (Sept. 5, 2017).

<sup>101</sup> Elizabeth M. Mudge, Susan J. Murch & Paula N. Brown, *Leaner and greener analysis of cannabinoids*, 409 Analytical and Bioanalytical Chemistry 3153 (2017).

<sup>102</sup> *Cannabis Testing & Analysis with the Power of LC-MS/MS*, SCIEX, <https://sciex.com/applications/food-and-beverage-testing/cannabis-testing> (last visited May 22, 2019).

<sup>103</sup> *Comprehensive Cannabis Testing Solutions*, Agilent, <https://www.agilent.com/en/promotions/cannabis> (last visited May 22, 2019).

<sup>104</sup> *Growing Analytical Solutions for Cannabis Labs*, Restek, <https://www.restek.com/cannabis> (last visited May 22, 2019).

<sup>105</sup> *Cannabis Analysis*, Perkin Elmer, <https://www.perkinelmer.com/category/cannabis-analysis> (last visited May 22, 2019).

<sup>106</sup> *Complete solutions for cannabis testing*, Phenomenex, <https://phenomenex.com/Info/Page/17cannabis> (last visited May 22, 2019).

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ASTM Committee D37 is working on a standard for terminology relating to cannabis, WK60576, Standard for Terminology Relating to Cannabis.<sup>107</sup> This standard may be a useful reference when determining definitions.

To standardize the nomenclature used in the cannabis industry, it is recommended that, at a minimum, the following terms be defined. Example definitions are provided.

*Cannabis* means a genus of plants within the Cannabaceae family distinguished by upright stems, divided and serrated leaves, and glandular hairs. *Cannabis* includes low-THC (i.e. hemp) and high-THC Cultivars. *Hemp* means Cultivars of *Cannabis* containing no more than 0.3 percent of  $\Delta^9$ -THC-A on a dry weight basis.

*Hempseed* means the seeds of the *Hemp* plant.

*Hemp Oil* means the crude oil extracted from the grown, whole *Hemp* plants (not *Hempseed*) and includes cannabinoids (primarily CBD), terpenes, flavonoids, and other organic compounds.

*Hemp-Infused Product* means any product that is composed of *Hemp* and at least one other ingredient and is intended for use or consumption other than by smoking or vaping. A *Hemp-Infused Product* may be an *Ingestible Hemp-Infused Product* or a *Non-Ingestible Hemp-Infused Product*.

*Ingestible Hemp-Infused Product* or “*Ingestible*,” means a product that contains *Hemp* and at least one other ingredient, is intended for oral consumption and includes edibles, beverages, tinctures, and supplements.

*Non-Ingestible Hemp-Infused Product*, or “*Non-Ingestible*,” means a product that contains *Hemp* and at least one other ingredient, is intended for consumption or use other than by smoking or vaporizing, is intended for external use only, and is one of the following:

*Topical Hemp-Infused Product*, or “*Topical*,” which is a *Non-Ingestible Hemp-Infused Product* that is not Psychoactive when used as intended. *Topical Hemp-Infused Products* include but are not limited to *Hemp-infused* creams, salves, bath soaks, and lotions

*Transdermal Hemp-Infused Product*, or “*Transdermal*,” which is a *Non-Ingestible Hemp-Infused Product* that contains at least one skin-permeation-enhancing ingredient to facilitate absorption through the skin into the bloodstream. *Transdermal Hemp-Infused Products* include but are not limited to *Hemp infused adhesive patches* that are applied to the skin surface.

*Hempseed oil* means the cold-pressed oil extracted from *Hempseed* that is primarily made up of fatty acids, protein, carbohydrates, fiber, and trace minerals and does not contain any significant amounts of cannabinoids or terpenes.

*Cannabidiol (CBD)* means a non-intoxicating cannabinoid found in *Cannabis* plants and is one of the main constituents of *Hemp* plants.

*CBD Isolate* means the pure, crystalline powder that typically contains >95% CBD.

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<sup>107</sup> Subcommittee D37.91, *New Terminology for Standard for Terminology Relating to Cannabis*, ASTM WK60576 (Sept. 20, 2017), <https://www.astm.org/DATABASE.CART/WORKITEMS/WK60576.htm>.

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*CBD Distillate* means a highly refined Cannabis or Hemp extract that typically contains >80% CBD.

*Water-Soluble CBD* means CBD that is broken down into nanosized particles using nanotechnology so that the CBD becomes compatible with water.

*Cultivar* means a plant variety produced in cultivation by selective breeding.

*Cannabis Product* means a finished product intended for human consumption or use that is composed partially or completely of Cannabis. This term “Cannabis Product” is generally used to refer to one or more of the following: Cannabis Flower, Cannabis Concentrates, and Cannabis-Infused Products, including Ingestible Cannabis-Infused Products and Non-Ingestible Cannabis-Infused Products and all subcategories thereof.

*Cannabis Product Category* means a defined group of Cannabis Products that are in the same form. Cannabis Product Categories are as follows: Cannabis Flower, Cannabis Concentrates, and Cannabis-Infused Products.

*Cannabis Flower*, or “Flower,” means the inflorescence(s) of the mature pistillate (female) Cannabis plant.

*Cannabis Concentrate*, or “Concentrate,” means a substance obtained by separating naturally occurring chemical constituents of Cannabis, such as cannabinoids, from insoluble Cannabis plant material by mechanical, chemical, or other processes and that may (1) contain solvents in allowable amounts and ingredients used to promote a desired physical state, texture, or flavor in the Cannabis Concentrate, but no other ingredients, and be intended for use in the production of Cannabis-Infused Products; or (2) be a finished product intended for human consumption or use.

*Activated Concentrate* means Cannabis Concentrate that was intentionally subjected to conditions or processes that cause decarboxylation for the purpose of converting THC-A and CBD-A to Active THC and CBD.

*Non-Activated Concentrate* means a Cannabis Concentrate that was not intentionally subjected to conditions or processes that cause decarboxylation.

*Cannabis-Infused Product* means any Cannabis Product that is composed of Cannabis and at least one other ingredient and is intended for use or consumption other than by smoking or vaporizing. A Cannabis-Infused Product may be an Ingestible Cannabis-Infused Product or a Non-Ingestible Cannabis-Infused Product.

*Ingestible Cannabis-Infused Product*, or “Ingestible,” means a product that contains Cannabis and at least one other ingredient, is intended for oral consumption, and includes edibles, beverages, tinctures, and supplements.

*Non-Ingestible Cannabis-Infused Product*, or “Non-Ingestible,” means a product that contains Cannabis and at least one other ingredient, is intended for consumption or use other than by smoking or vaporizing, is intended for external use only, and is one of the following:

*Topical Cannabis-Infused Product*, or “Topical,” which is a Non-Ingestible Cannabis-Infused Product that is not psychoactive when used as intended. Topical Cannabis-Infused Products include but are not limited to Cannabis-infused creams, salves, bath soaks, and lotions.

*Transdermal Cannabis-Infused Product*, or “Transdermal,” which is a Non-Ingestible Cannabis-Infused Product that contains at least one skin-permeation-enhancing ingredient to facilitate

absorption through the skin into the bloodstream and may be psychoactive when used as intended. Transdermal Cannabis-Infused Products include but are not limited to Cannabis-infused adhesive patches that are applied to the skin surface.

**5. What are the functional purposes of adding cannabis-derived compounds, such as CBD, to foods (eg: nutritional value, technical effect), both in terms of manufacturer intent and consumer perceptions and/or expectations? To the extent a compound is added to food to achieve a particular functional purpose, what evidentiary support is available to demonstrate that the addition of such compound has the intended or perceived effect?**

In recent years, a focus on healthier eating has drawn attention to hempseed and food products containing ingredients derived from cannabis. We know about the nutritional benefits of hempseed in foods as a great source of protein, fiber, and essential polyunsaturated fatty acids including linoleic ( $\omega$ -6) and  $\alpha$ -linolenic acids (ALA) ( $\omega$ -3).<sup>108</sup> Now, foods with other cannabis-derived compounds such as CBD, THC, and terpenes are more desired.

The manufacturer's intent in adding cannabis-derived compounds to food is that it may enhance the food's functional effect on a person's health and wellbeing as well as improve the food's aroma and flavor. The consumer's perception of consuming CBD and other cannabis-derived compounds in foods is that it may provide functional wellness and health benefits, similar to perceptions of consuming probiotics in kombucha, omega fatty acids in fish, or flavonoids in other foods. They may also expect cannabis-infused foods to have special aromatic and flavor properties, enhanced by the naturally derived terpene blends contained within different cannabis cultivars.

***Cannabinoids***

Cannabinoids are known to affect the endocannabinoid system (ECS). They can work synergistically with terpenes to produce an "entourage effect" for enhanced modulation of the ECS.<sup>109</sup> The ECS is considered to function in relaxation, eating, sleeping, memory, metabolism, and inflammation, making it a major regulatory homeostatic system of the body.<sup>110, 111, 112, 113, 114,</sup>

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<sup>108</sup> J.C. Callaway, *Hempseed as a nutritional resource: An overview*, 140 *Euphytica* 65 (Jan. 2004).

<sup>109</sup> Ethan B. Russo, *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects*, 163 *British Journal of Pharmacology*, 1344 (Aug. 2011).

<sup>110</sup> S.F. Lisboa et al., *The Endocannabinoid System and Anxiety*, 103 *Vitamins and Hormones* 193 (2017).

<sup>111</sup> Benjamin K. Lau et al., *Endocannabinoid modulation of homeostatic and non-homeostatic feeding circuits*, 124 *Neuropharmacology* 38 (Sept. 15, 2017).

<sup>112</sup> Eric Murillo-Rodriguez et al., *The Emerging Role of the Endocannabinoid System in the Sleep-Wake Cycle Modulation*, 11 *Central Nervous System Agents in Medicinal Chemistry* 189 (2011).

<sup>113</sup> Marta Kruk-Slomka et al., *Endocannabinoid System: The Direct and Indirect Involvement in the Memory and Learning Processes—a Short Review*, 54 *Molecular Neurobiology* 8332 (2017).

<sup>114</sup> Jeffrey Kim, Yong Li & Bruce A. Watkins, *Endocannabinoid signaling and energy metabolism: A target for dietary intervention*, 27 *Nutrition* 624 (2011).

<sup>115</sup> There are several plant-derived compounds in common foods, herbs, and spices that have been recently discovered to modulate the ECS in addition to CBD and THC. Examples include falcarinol in carrots, capsaicin in chili peppers, gingerol and zingerone in ginger, piperine in black pepper, curcumin in turmeric, and anandamide in black truffles.<sup>116</sup> Supplying our ECS with compounds in foods that modulate it can be a lifestyle strategy to “care for and feed the ECS,” much like we consume proteins in food to feed our muscles.<sup>117</sup>

However, scientific research of the functional purposes of cannabis-derived compounds specifically in food is limited to hempseed food products due to legal roadblocks. Anecdotal evidence demonstrates that CBD and other cannabinoids’ benefits are associated with general good health and wellness. For example, consuming CBD has been said to make people feel calm and less stressed and to provide pain and digestive relief, among other effects. This could be why CBD and other cannabis-derived compounds may be desired in foods as an easy lifestyle strategy to benefit homeostasis in our bodies while also providing nutrition.

### **Terpenes**

Terpenes are commonly found in cannabis and other plants and are widely used as flavoring ingredients in the food industry because of their smell and taste. Terpenes have been recognized by the U.S. Food and Drug Administration as Generally Recognized as Safe (GRAS) ingredients.<sup>118</sup> For example, a lemon-flavored food might include the terpene limonene to impart the citrus aroma and flavor of real lemon without the added acidity. Also, the antimicrobial properties of some terpenes have created growing interest in using them as natural additives in foods, in addition to traditional preservatives or techniques, to reduce the risk of pathogen and spoilage organism contamination.<sup>119</sup>

## **Marketing/Labeling/Sales**

- 1. How should consumers be informed about the risks associated with such products (e.g., directions for use, warnings)? What specific risks should consumers be informed about? Are there any subpopulations for which additional warnings or restrictions are appropriate? Please explain your reasoning.**

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<sup>115</sup> Renger Witkamp Jocelijn Meijerink, *The endocannabinoid system: An emerging key player in inflammation*, 17 *Current Opinion in Clinical Nutrition and Metabolic Care* 130 (Mar. 2014).

<sup>116</sup> Ethan B. Russo, *Beyond cannabis: plants and the endocannabinoid system*, 37 *Trends in Pharmacological Sciences* 594 (2016).

<sup>117</sup> John M. McPartland, Geoffrey W. Guy & Vincenzo Di Marzo, *Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System*, 9 *PLOS One* e89566 (Mar. 12, 2014).

<sup>118</sup> T.B. Adams, et al., *The FEMA GRAS assessment of aliphatic and aromatic terpene hydrocarbons used as flavor ingredients*, 49 *Food and Chemical Toxicology* 2471 (2011).

<sup>119</sup> Ignacio Gutiérrez-del-Río, Javier Fernández, & Felipe Lombó, *Plant nutraceuticals as antimicrobial agents in food preservation: terpenoids, polyphenols and thiols*, 52 *International Journal of Antimicrobial Agents* 309 (2018).

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CBD is nontoxic, nonaddictive, and safe for humans, even in high doses.<sup>120</sup> Risks are especially mitigated for CBD products that are produced in compliance with cGACP and cGMP standards—i.e., in controlled food-safe or lab environments, using safe and verified extraction processes, from hemp biomass that has been cultivated in rich, healthy, and uncontaminated soils. Risks of side effects should be managed by ensuring that cannabinoid-infused products are being produced in accordance with standard state mandated safe food handling and manufacturing practices, which are regulated by each state’s department of agriculture.

Additionally, risk potential is greatly reduced where products are subject to standard regulated adult-use cannabinoid testing laws (most notably as currently defined in the states of Colorado and Oregon). These testing and compliance procedures protect consumers from exposure to residual solvents, bio-contaminants, and pesticides, fungicides, and heavy metals, which could all potentially be present in the hemp cannabinoid plant material (biomass) and therefore in the hemp extracts and/or concentrates that are used in the manufacturing of cannabinoid-infused products. State mandated testing procedures also serve to ensure and verify accurate cannabinoid potency in biomass/concentrates/extracts and in finished cannabinoid-infused products, which is necessary to accurately inform consumers of how many milligrams and what types of active cannabinoids they are consuming in any given product and in each specified serving.

Currently, due to the mostly unregulated or unenforced nature of the non-psychoactive cannabinoid products industry, manufacturers and distributors may (intentionally or not) make misleading claims to consumers. Active cannabinoid content should be clearly stated in the Supplement Facts panel, Nutritional Facts panel, or list of cosmetics ingredients on these products. Currently, some companies are stating cannabinoid content on packaging in ways that could mislead consumers. For example, a product may state on its label that it contains “3,000 milligrams” in a way that implies that the number refers to the active cannabinoid content in the product (or per serving), while what the product actually contains is 3,000 mg of hemp oil, extract, or concentrate. Furthermore, the active cannabinoid content can vary dramatically among different types of hemp oil, extract, or concentrate—a food-grade hempseed oil may include only trace amounts of active cannabinoids, while a crude whole plant hemp extract may contain far more active cannabinoids.

Additionally, even identifying active cannabinoid content may be confusing without labeling what types of cannabinoids are present. Some full-spectrum products may include only trace amounts of CBD relative to other active cannabinoids, while a high potency hemp cannabinoid isolate may consist entirely of a single cannabinoid. Moreover, while including trace amounts of THC may be lawful, consumers who remain wary of ingesting THC should be able to determine how much THC content is included in a product and in each individual serving or application. So, it is imperative that active cannabinoid content be clearly stated on product labels, with accurate serving recommendations or application instructions, so consumers can monitor their intake of active cannabinoids. Additionally, in order to comply with state and federal truth-in-advertising mandates, the source of the cannabinoids should be clearly identified—e.g., whether the cannabinoids are derived from broad-spectrum hemp extract (with permissible trace amounts

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<sup>120</sup> Mateus Machado Bergamaschi, et al., *Safety and side effects of cannabidiol, a Cannabis sativa constituent*, 6 Current Drug Safety 237 (Sept. 1, 2011).

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of THC), a refined hemp extract distillate (with one or more compounds, such as THC, completely removed), or CBD isolate (to the extent the FDA permits the sale of such isolates).

The risk profile for CBD-infused products in particular is extremely low, and side effects are very rare in most populations. However, some studies have shown that CBD may inhibit the essential liver enzyme system known as cytochrome P450.<sup>121</sup> CBD may inhibit the system's ability to metabolize certain non-cannabinoid drugs, leading to an overall increase in processing times. Grapefruit, watercress, St. John's wort, and goldenseal all have a similar impact. This can lead to higher levels of certain drugs in the system at one time, causing unwanted side effects and, in some cases, potential overdose of the non-cannabinoid drugs. If a patient is taking certain medications that can be affected by high doses of CBD, patients should be advised to consult with a doctor first and may need to adjust CBD dosage levels so that both products can safely be consumed together. As an additional precaution, pharmaceutical manufacturers should be required to disclose any risk of drug interactions with CBD in the same manner as they are currently required to do for other OTC drugs and dietary supplements.

Overall, there is an extremely low risk of side effects for non-psychoactive cannabinoid-infused products when managed with proper regulatory oversight of manufacturing and testing protocols that protect consumers from contamination. Additionally, when CBD and other non-psychoactive cannabinoid-infused products (including flowers, dietary supplements, foods, beverages, topicals, cosmetics, suppositories, patches, vapes, and other products) are taken in low and reasonable doses, the risks are almost nonexistent.

- 2. What conditions, restrictions, or other limitations on the manufacturing and distribution of these products have been put in place under State or local law, particularly with respect to food products containing cannabis-derived compounds such as CBD (which may, in some cases, be lawful at the State level but not the Federal level)? What other conditions, restrictions, or other limitations might be appropriate to ensure adequate consumer information and to protect the public health?**

**A. The Path Forward for Federal Regulation of Food Products Containing Cannabis-Derived compounds Such as CBD**

On December 20, 2018, President Trump signed into law the Agriculture Improvement Act of 2018<sup>122</sup> (2018 Farm Bill). Among other things, the 2018 Farm Bill removed hemp from the definition of "marihuana" (marijuana) in the Controlled Substances Act (CSA), thus taking it out of Schedule I.<sup>123</sup> Prior to being removed from Schedule I, hemp was treated as a drug with a high

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<sup>121</sup> See, e.g., Satoshi Yamaori et al., *Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: Role of phenolic hydroxyl groups in the resorcinol moiety*, 88 *Life Sci.* 730 (Apr. 11, 2011).

<sup>122</sup> Agriculture Improvement Act of 2018, Pub. L. No. 115-334.

<sup>123</sup> Controlled Substances Act, 21 U.S.C. § 802(16) (2016).

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potential for abuse, no accepted medical use, and a lack of accepted safety for use under medical supervision.<sup>124</sup>

By way of background, the Agricultural Act of 2014 (P.L. 113-79) (2014 Farm Bill) authorized states to establish agricultural pilot programs or other agricultural or academic research programs to study the growth, cultivation, or marketing of “industrial hemp.”<sup>125</sup> The 2014 Farm Bill defined industrial hemp as “the plant *Cannabis sativa* L. and any part of such plant, whether growing or not, with a delta-9 tetrahydrocannabinol [THC] concentration of not more than 0.3 percent on a dry weight basis.”<sup>126</sup> Despite the 2014 Farm Bill’s authorization to states to establish hemp pilot programs, the legislation did not specifically address the Schedule I status of hemp. In contrast, the 2018 Farm Bill amended the CSA to state that the term marijuana does not include hemp.<sup>127</sup> In addition, the 2018 law also amended the definition of hemp in the Agricultural Marketing Act of 1946,<sup>128</sup> with the result being an expansion of the definition referenced in the 2014 Farm Bill. It is now clear that hemp is no longer federally illegal under the CSA, but it is also clear that the phrase “any part of the plant” includes “the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers.”<sup>129</sup> This definition expansion is significant, given its inclusion of hemp-derived cannabinoids (e.g., CBD).

One of the biggest misconceptions coming out of the enactment of the 2018 Farm Bill is the idea that, now that hemp is legal, people can do whatever they want with it and its derivatives. While the 2018 Farm Bill is significant and will open up national and international hemp markets, there continue to be restrictions on what can be done with hemp and hemp derivatives (e.g., hemp-derived CBD). This is especially true when it comes to the addition of CBD or THC to certain products regulated by the U.S. Food and Drug Administration (FDA) (e.g., conventional foods and dietary supplements).

In response to the 2018 Farm Bill being signed into law, then-FDA Commissioner Scott Gottlieb, M.D., was quick to remind the public about what the 2018 Farm Bill did not change: the FDA’s authority to regulate products containing cannabis or cannabis-derived compounds under the Federal Food, Drug, and Cosmetic Act (FDCA) and section 351 of the Public Health Service Act.<sup>130</sup> While this is not surprising to those who carefully read the text of the 2018 Farm Bill,

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<sup>124</sup> *Id.* at § 816(b)(1).

<sup>125</sup> Agricultural Act of 2014, Pub L. No. 113-79.

<sup>126</sup> *Id.*

<sup>127</sup> *See supra*, note 119.

<sup>128</sup> *Id.*; *see also* Agricultural Marketing Act of 1946, Pub. L. No. 79-733.

<sup>129</sup> *See supra*, note 119.

<sup>130</sup> Press release, Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency’s regulation of products containing cannabis and cannabis-derived compounds (Dec. 20, 2018), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys?source=techstories.org>; and Press release, Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to advance agency’s continued evaluation of potential regulatory pathways for cannabis-containing and cannabis-derived products (Apr. 2, 2019), [https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation?mod=article\\_inline](https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-advance-agencys-continued-evaluation?mod=article_inline).

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which specifically preserves the FDA's authority, or to those that read the FDA's response to the 2014 Farm Bill, it is nonetheless a very important nuance.

The FDA's restrictions on adding CBD to products it regulates remain in place. More specifically, it is unlawful under the FDCA to introduce food containing added CBD or THC into interstate commerce or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived.<sup>131</sup> This is because both CBD and THC are active ingredients in FDA-approved drugs and were the subject of substantial clinical investigations before they were marketed as foods or dietary supplements. Under the FDCA, it is illegal to introduce drug ingredients like these into the food supply, and they are not permissible ingredients in dietary supplements.

While the FDA has articulated its views on the impermissibility of adding CBD and THC to certain products that it regulates, the FDA should now take steps to properly distinguish between CBD isolate and non-standardized hemp extract that contains naturally occurring cannabinoids, including CBD. While it seems reasonable to conclude that investigational study of CBD isolate, which occurred in 2006, predated CBD being marketed as a dietary supplement, it is also reasonable to conclude that hemp has been in foods for well over 100 years.

In evaluating whether non-standardized hemp extract that contains naturally occurring CBD may be marketed as conventional foods or dietary supplements, it is helpful to review the well-known case of *Pharmanex v. Shalala*,<sup>132</sup> to which a number of parallels can be drawn. At issue in *Pharmanex* was whether manufactured increases in lovastatin in red yeast rice dietary supplements was permissible, given that lovastatin was approved by the FDA as a drug prior to its being present in foods. Tortured procedural history aside, and despite *Pharmanex* ultimately losing the case, the FDA has allowed marketers of red yeast rice to continue to market such products, so long as the formulations are not standardized (i.e., without artificially increased levels of lovastatin).

Applying the same logic, the FDA should allow marketers of non-standardized hemp extracts that contain naturally occurring CBD (and other cannabinoids) to market such products as conventional foods and dietary supplements, given that hemp (and the cannabinoids naturally contained in the same) has been present in the food supply for well over 100 years. The ability of firms in this space to market non-standardized hemp extracts presumes that they do not make therapeutic claims regarding such products. If they did, such products would be regulated as drugs and would require premarket approval.

In addition to allowing consumers to continue to benefit from the myriad product offerings in this space without interruption for regulatory review—which is not needed, given that hemp products have been consumed without incident for over 100 years—the red yeast rice approach has the added benefit of not requiring the FDA to take years to go through the notice-and-comment rulemaking process.

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<sup>131</sup> Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301.

<sup>132</sup> *Pharmanex v. Shalala*, 221 F.3d 1151 (10th Cir. 2000).

**B. Summary of Conditions, Restrictions, and Other Limitations on the Manufacturing and Distribution of Food Products Containing Cannabis-Derived Compounds Such as CBD Under Existing State Laws**

**1. Multiple and Varied Statutory Schemes Under Current State Laws**

Because CBD and other cannabinoid-rich compounds may be derived from either “industrial hemp” or “marijuana” (delineated by the THC content, as per federal law), different regimes on the manufacture and distribution of food products containing cannabis-derived compounds may coexist within the same state, dependent entirely on the type of cannabis plant (> 0.3% THC, or not) used to extract the compound. Some states have laws legalizing possession and/or access to CBD derived from marijuana (and/or low-THC/CBD-rich cannabis), which may or may not address manufacturing and distribution of extracts and/or food products and may or may not prohibit such activity within the state. Some states have industrial hemp programs that generally allow the “processing” of hemp but may or may not expressly contemplate the manufacture and distribution of plant extracts, and if they do, they may or may not address CBD specifically.

Additionally, states with medical and/or adult-use marijuana laws may or may not permit the manufacture and distribution of marijuana extracts (including CBD isolates and CBD-rich concentrates), and these states may or may not also have industrial hemp laws. Within those states that have both hemp and marijuana laws, they may or may not permit the incorporation of hemp extracts or hemp-derived CBD in the supply chain for the manufacture of THC-infused edible products.

Given the broad variety in state statutory schemes that address the manufacture and distribution of food products containing cannabis-derived compounds, and such schemes’ interaction with one another in some states, we endeavor to discuss only the most helpful exemplars below, rather than attempting to present the FDA with an exhaustive survey of all potentially applicable exemplars.

**2. State Hemp Laws**

**a. Example 1 from Legal Hemp States: Washington**

Washington enacted SB 5276 on April 26, 2019. SB 5276 makes hemp (as defined in the 2018 Farm Bill) “an agricultural product that may be legally grown, produced, *processed*, possessed, *transferred*, *commercially sold*, and *traded*” (emphasis added). Washington state law explicitly provides for the regulation of “the processing of hemp for food products, *that are allowable under federal law*, in the same manner as other food processing under [Washington law] and may adopt rules . . . for food products including, but not limited to, establishing standards for *creating hemp extracts used for food*” (emphasis added). Because the Washington State Department of Agriculture (WSDA) has yet to promulgate rules implementing SB 5276, it is uncertain how the WSDA will define “allowable under federal law” in terms of CBD-infused food—i.e., whether the WSDA will adopt the FDA’s current prohibitions on the addition of CBD

isolate to food or adopt the approach of permitting broad-spectrum hemp extract (with naturally occurring levels of CBD as well as other cannabinoids) under the *Pharmanex* precedent.

**b. Example 2 from Legal Hemp States: Alaska**

Alaska law (pursuant to SB 6, enacted on April 13, 2018) provides for the creation of an industrial hemp pilot program (AK Hemp Program) under the Alaska Department of Natural Resources (ADNR). Under the AK Hemp Program, a program registrant may “produce industrial hemp, including growing, harvesting, possessing, *transporting, processing, selling, or buying* industrial hemp” (emphasis added). Alaska also removed “cannabidiol oil” from the definition of “hashish oil” in its state-controlled substances act. Most notably, Alaska amends the Alaska Food, Drug, and Cosmetic Act by specifying that “(f)ood is not adulterated under this section solely because it contains industrial hemp, . . . or an industrial hemp product.” State law thus expressly contemplates manufacturing and distributing food infused with “CBD oil” produced under the AK Hemp Program within Alaska. That said, Alaska state regulators also defer to federal guidance; according to an FAQ page<sup>133</sup> on ADNR’s website, ADNR:

*expect[s] that so long as CBD is processed from industrial hemp produced by registrations participating in the pilot program, it will be legal for program registrants to sell. However, DNR and the Department of Law will continue to address how changing federal law might restrict legal production of CBD-containing products, even under a pilot program.*

According to the same page (updated June 15, 2018), ADNR has yet to promulgate regulations under SB 6. Therefore, it remains uncertain how the manufacture and distribution of hemp-derived CBD-infused foods will ultimately be regulated.

**c. Example 3 from Legal Hemp States: Missouri**

Missouri law created an industrial hemp agricultural pilot program (MO Hemp Program) under the Missouri Department of Agriculture pursuant to HB 2034, effective August 28, 2018. Under state law, an MO Hemp Program registrant may “grow, harvest, cultivate, and *process* industrial hemp.” The bill does not explicitly provide for the commercial sale of industrial hemp or industrial hemp products; similarly, proposed regulations<sup>134</sup> pursuant to HB 2034 do not explicitly provide for commercial sales, although multiple rules contemplate sales (e.g., regarding a “hemp plant monitoring system” that keeps records including for the “sale or distribution of industrial hemp”). Most notably, HB 2034 amended Missouri’s food safety law: “A food shall not be considered adulterated solely for containing industrial hemp, *or an industrial hemp commodity or product*” (emphasis added). This suggests that, to the extent that commercial industrial hemp sales are allowed, allowable sales include CBD-infused food. The MO Hemp Program will not formally commence until applications are made available on September 3, 2019.

<sup>133</sup> See *FAQs Regarding Alaska’s Industrial Hemp Pilot Program*, State of Alaska Department of Natural Resources (June 15, 2018), <http://plants.alaska.gov/industrialhempFAQs.htm>.

<sup>134</sup> See 44 Mo. Reg. 38 (Jan. 2, 2019), <https://www.sos.mo.gov/CMSImages/AdRules/moreg/2019/v44n1Jan2/v44n1b.pdf>.

### **3. Relevance of State Medical and/or Adult Use Marijuana Laws**

Given that the manufacture and sale of CBD derived from psychoactive cannabis (> 0.3% THC) is not before the FDA, and the market is not being flooded with these types of infused products, we acknowledge at the outset that not all cannabis laws have applicability. That said, the fact that these CBD products are limited to consumers with qualified health conditions and/or aged 21 years and older is only a function of the continued Schedule I status of the underlying source material from which they are derived; it is not an indication by any jurisdiction that such CBD products should be limited to those populations for public health reasons. However, state marijuana laws do contemplate some conditions, restrictions, and other limitations on the manufacturing and distribution of cannabis-derived compounds (including low-THC/CBD-rich compounds and food products containing them) *other* than age limits or a physician's recommendation, which could provide useful guidance to the FDA. Specifically, marijuana laws mandating testing of plant extracts and cannabinoid-infused foods, and clarifying that cannabis is not an adulterant when added to food products, often have analogs in state hemp laws and may be applied to hemp extracts in states with both legal marijuana and hemp processing laws. We see this principle applied in states like Oregon, which subjects hemp extracts with naturally occurring CBD (as well as hemp-derived CBD isolate) to the same testing and consumer safety requirements as marijuana extracts.

#### **a. Limited Relevance of State CBD-Only Laws**

It is important to clarify that when we refer to state CBD laws, we are referring to laws other than state analogs to the FDCA. That said, these laws have limited relevance to the FDA's query and are not discussed separately from state marijuana laws for the following reasons. Like state medical marijuana laws, state CBD-only laws restrict lawful possession to those with qualified medical conditions and apply to products that are derived from marijuana (and/or low-THC/CBD-rich cannabis, which may still qualify as marijuana under federal law); additionally, CBD-only laws were promulgated to establish a defense to criminal prosecution for possession of CBD derived from marijuana, and most do not actually address the manufacture and distribution of CBD. Even among those laws that do address how patients access marijuana-derived CBD products (e.g., Texas and Virginia), some actually prohibit the manufacture and distribution of food products infused with CBD (e.g., Iowa and North Carolina), and some even prohibit manufacture or distribution of any plant extracts within the state (e.g., North Carolina, Tennessee, and Utah), thus offering no guidance for the FDA's purposes.

#### **b. Example 1 from Medical and/or Adult-Use Marijuana States: Oregon**

Oregon provides for the lawful manufacturing and distribution of (hemp-derived) CBD-infused food under two distinct but overlapping regulatory schemes: (1) an Oregon Department of Agriculture (ODA) industrial hemp pilot program (OR Hemp Program) pursuant to the 2018

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Farm Bill and 2014 Farm Bill; and (2) an adult-use marijuana regulatory program administered by the Oregon Liquor Control Commission (OLCC) (OR Marihuana Program).<sup>135</sup>

Under the OR Hemp Program, the ODA regulates the cultivation and processing of industrial hemp (the plant and derivatives of the plant *Cannabis sativa L.* containing 0.3% THC or less by dry weight)—including commercial activity thereof—through issuance of grower and handler (processor) registrations. Once industrial hemp biomass has been converted into an “industrial hemp product or commodity” (e.g., hemp extract or CBD isolate), the ODA no longer retains regulatory authority over the resultant product, with the key exception of *required potency, solvent, and pesticide testing* prior to sale of a finished product to a consumer. Consequently, a hemp handler registration is not required to infuse processed hemp into a food product after it has been tested. The OR Hemp Program allows for the addition of hemp-derived CBD to food based on a statutory provision that excludes “industrial hemp” and “industrial hemp commodities” from the definition of “adulterant” under Oregon food safety law.<sup>136</sup> Oregon law does not restrict the retail sale of industrial hemp products or commodities—including CBD-infused food—to any specially approved or licensed retail outlet. Nor does the OR Hemp Program require any hemp-specific packaging or labeling. The OR Hemp Program also allows for the general exportation of industrial hemp and industrial hemp products and commodities and the importation of the same if the hemp or hemp product meets or exceeds ODA requirements.

Under the OR Marihuana Program, an ODA registrant with an “OLCC certificate” may transfer industrial hemp biomass or products or commodities to certain OLCC marijuana licensees (i.e., processors with a hemp endorsement, wholesalers, or retailers). To do so, the registrant must adopt OLCC’s approved seed-to-sale tracking system and properly track and manifest each transfer. Once the hemp enters the OLCC system, it must remain in the system (i.e., it can only be transferred to another OLCC licensee or sold to a consumer through an OLCC-licensed retailer) and cannot leave the state. All industrial hemp and hemp products or commodities within the OLCC system are subject to *potency, solvent, and pesticide* testing required of the marijuana equivalent of the hemp product. Applicable OLCC licensees may add hemp-derived CBD to food items under the same statutory provision referenced above. OLCC also requires that all hemp-derived items meet the same packing and labeling requirements (including child-resistant packaging) as marijuana items—including affixing the “universal hemp symbol” to the label.

**c. Example 2 from Medical and/or Adult Use Marihuana States:  
California**

Like Oregon, California has legalized both industrial hemp and marijuana, and it has statutes and regulations governing the manufacture and distribution of products derived from both. However, unlike Oregon, California regulations promulgated under its Medicinal and Adult-Use Cannabis Regulation and Safety Act (MAUCRSA) do not permit the manufacturing and distribution of industrial hemp products by licensed marijuana businesses, and all CBD extracts and isolates

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<sup>135</sup> Technically, Oregon law provides for the manufacture and distribution of marijuana-derived CBD-infused food products under its medical marijuana program administered by the Oregon Health Authority, but this accounts for a de minimis percentage of CBD-infused foods in Oregon.

<sup>136</sup> Or. Rev. Stat. § 571.303(2).

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must be derived from marijuana to be lawfully manufactured, stored, transported, distributed, or sold. MAUCRSA defines “cannabis” to exclude “industrial hemp,” and hemp-CBD extracts and isolates are deemed “non-cannabis” products.

California’s industrial hemp laws and regulations do not explicitly address processing or extraction of hemp-derived CBD products—only growing and harvesting. In July 2018, California’s Department of Public Health (CDPH) announced that the infusion of hemp-derived CBD isolate in food products in California was prohibited under California’s Sherman Food, Drug, and Cosmetic Act, based on the FDA’s determination that CBD is deemed a “drug” subject to the federal FDCA:

[A]lthough California currently allows the manufacturing and sales of cannabis products (including edibles), the use of industrial hemp as the source of CBD to be added to food products is prohibited. Until the FDA rules that industrial hemp-derived CBD oil and CBD products can be used as a food or California makes a determination that they are safe to use for human and animal consumption, CBD products are not an approved food, food ingredient, food additive, or dietary supplement.<sup>137</sup>

CDPH did not take any clear position on the infusion of broad-spectrum hemp extract into foods at that time, nor did it update its guidance after passage of the 2018 Farm Bill. Thus, to the extent that the *Pharmanex* precedent is applicable to such products at the federal level, the same would presumably apply in California.

3. **What statutory or regulatory restrictions are in place under State or local law to warn about the use of these products by certain vulnerable human populations (e.g., children, adolescents, pregnant and lactating women) or animal populations (e.g. species, breed, or class)? Are there other steps that should be taken to warn about use by vulnerable populations? Please identify such steps and how they would apply to a particular subpopulation.**

- A. **Statutory and Regulatory Restrictions to Warn About Products Vulnerable to Human Populations**

States and municipalities warn consumers about the risks associated with CBD that is sold through regulated medical and recreational marijuana dispensaries throughout the sales lifecycle, including through the use of (1) in-store disclaimers; (2) disclosures in advertising; (3) point-of-sale disclosures; and (4) product label disclosures. States and municipalities often target persons who may be vulnerable or at risk, such as patients, pregnant women, children, and all persons who may experience adverse side effects.

Examples of the risk disclosures required by states and municipalities include:

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<sup>137</sup> See *FAQ – Industrial Hemp and Cannabidiol (CBD) in Food Products*, California Department of Public Health (last revised July 6, 2018), <https://www.cdph.ca.gov/Programs/CEH/DFDCS/CDPH%20Document%20Library/FDB/FoodSafetyProgram/HEMP/Web%20template%20for%20FSS%20Rounded%20-%20Final.pdf>.

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- “This product has not been analyzed or approved by the United States Food and Drug Administration. There is limited information on the side effects of using this product, and there may be associated health risks and medication interactions. This product is not recommended for use by pregnant or breastfeeding women. **KEEP THIS PRODUCT OUT OF REACH OF CHILDREN.**”<sup>138</sup>
- “This medical cannabidiol is for therapeutic use only. Use of this product by a person other than the patient listed on the label is unlawful and may result in the cancellation of the patient’s medical cannabidiol registration card. Return unused medical cannabidiol to a dispensary for disposal.”<sup>139</sup>
- “This product is derived from hemp and could contain THC. Keep out of reach of children.”<sup>140</sup>
- “If the item is a hemp extract, concentrate, topical, or a hemp product other than an edible, tincture, or capsule, the label shall contain the warning, “**DO NOT EAT**” in bold, capital letters.”<sup>141</sup>
- “Statement that the product is for medical use only and is intended for the exclusive use of the patient to whom it is prescribed. This statement should be in bold print.”<sup>142</sup>
- “That ingesting marijuana or marijuana products with alcohol or other drugs, including prescription medication, may result in unpredictable levels of impairment and that a person should consult with a physician before doing so.”<sup>143</sup>
- “For use only by the person named on the label of the dispensed product. Keep out of reach of children.”<sup>144</sup>
- “The cannabinoid profile and concentration levels and terpenoid profile as determined by the testing laboratory.”<sup>145</sup>

#### **B. Alternative Steps for Warning Vulnerable Populations**

In lieu of or in addition to the warnings described above, there are means of educating the public, generally, about the risks of CBD products. Examples of the same might include government-sponsored public service announcements, educational campaigns, and required uniform risk disclosures.

- a. Public Service Announcements—States that allow the production, sale, and distribution of CBD products could use tax revenue from sales of the same to create public service announcements that educate residents about CBD and associated risks.

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<sup>138</sup> Iowa Admin. Code r. 154.21(3).

<sup>139</sup> *Id.*

<sup>140</sup> Or. Admin. R. 845-025-7140 (2018).

<sup>141</sup> *Id.*

<sup>142</sup> 37 Tex. Admin. Code §12.7.

<sup>143</sup> Nev. Rev. Stat. § 453D.310 (Effective Jan. 1, 2010).

<sup>144</sup> Ohio Admin. Code 3796:6-3-09 (2017).

<sup>145</sup> Nev. Admin. Code § 453D.816 (2018) (Nev. Rev. Stat. § 453D.200 (2016)).

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- b. Educational Campaigns—Industry groups such as the NCIA can sponsor educational campaigns and events to educate people about how CBD can adversely affect vulnerable populations.
- c. Uniform Risk Disclosure—Uniform risk disclosures might help ensure that all CBD products contain the same level of disclosure so that, when faced with product choices, consumers can compare products on an “apples to apples” basis.

**4. What other information should FDA consider in the labeling of specific product categories of cannabis and cannabis-derived products?**

The cannabis-derived products industry has largely managed to successfully self-regulate through transparent product labeling practices that relate to both product quality and product safety. The following are but a few examples of labeling practices commonly used on products in this space:

- Product labeling indicates CBD source and relates to the product certificate of analysis (COA). Some examples include:
  - Derived from CBD Isolate
  - Derived from CBD Distillate
  - Derived from CBD Crude Oil/ Raw Hemp Extract
  - Derived from Water Soluble CBD

This disclosure references the type of actual ingredient being used, whether it is made for consumption or topical use. This disclosure directly correlates with how the product can potentially perform and implicates the various molecular structures of these various forms, because they are not all equal in phytoactivity or therapeutic value.

- Products state the milligram (mg) content and CBD potency by percentage.

Such information allows consumers to select and use products responsibly. We would also note that, as part of states’ oversight of this space, third-party testing is performed. Such testing results will show how “active” the CBD material in the product is. This is commonly measured in a percentage (e.g., 30% total active cannabinoid levels, 20% CBD). Using label standard examples similar to the percentage of alcohol concentration found in various products will guide consumers in transparent, safe purchasing of CBD-derived products.

For example, in the state of Utah, CBD products must go through a state registration program to be used as a topical during a massage or sold at retail. One way to increase transparency in this space is for manufacturers to include on product labeling a scannable code (e.g., a QR code) that would link directly to the corresponding COA and/or third-party laboratory testing results.

- Keep out of direct sunlight and extended temperatures that could exceed 120 degrees F.

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Direct exposure to sunlight and high temperatures is known to cause a breakdown in the structure and integrity of phytoactives, defeating the intended use of both topical and consumable products.

One related point is that microbial testing on topical, cannabis-derived products is largely unregulated. More information is needed with regard to whether or not topical CBD products can withstand deterioration, and if they cannot, what the relationship is between deterioration and microbial content. Due to the basic biological mechanisms represented in research of how CBD engages with the body, topical products that have not undergone microbial testing could potentially cause unwanted effects to the skin or deeper connective tissue layers. To be certain a CBD topical product formulation is safe after being exposed to various harmful microbes, further study is needed. In the meantime, topical products may require microbial testing to ensure consumer safety.

## **NCIA’S PRIOR WORK ON LAB TESTING AND MARKETING/LABELING**

In January 2017, the National Cannabis Industry Association created the NCIA Policy Council to serve as the industry’s policy “think tank” and lead the development of thoughtful policy recommendations for the post-prohibition era. Policy Council members provide critical insights to NCIA’s staff and Board on important policy matters that shape the future of the industry for years to come, from determining the ideal federal tax structure to informing state leaders on model regulations. In July 2018, the NCIA Policy Council released the report *Cannabis Testing Policy: Recommendations for More Thoughtful and Consistent Regulations*. This report was later followed by *Cannabis Packaging and Labeling: Recommendations for Sensible and Consistent Regulations Across States and Nations* in February 2019. We hope that these two reports, one on cannabis testing and the other on packaging and labeling, provide valuable insights and information for the FDA as it undergoes rulemaking to establish public health and safety guidance for new cannabinoid products.

Both policy papers represent months of work from a coalition of experts inside and outside of the cannabis industry. The drafting process for each paper started with the establishment of a multi-stakeholder working group and the accumulation of existing data and resources on federal regulation of similar products. Analyzing existing regulatory structures for similar products provided a foundation for understanding how states and federal agencies protect public health and safety by establishing production standards for consumer goods. Once the most relevant regulatory issues were fully understood, the expert working group discussed the real-world implications of different testing, packaging, and labeling regulations. In most cases these conversations led to the development of consensus regulatory models for national standards. These standards were then formulated into recommendations for policymakers and, in the case of the packaging and labeling paper, model regulations that state and federal departments can adopt outright.

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The following comments summarize the most important recommendations and datapoints contained within the NCIA Policy Council's testing paper and labeling and packaging paper. While these two documents primarily focus on state-regulated medical and adult-use cannabis programs, the NCIA hopes that the recommendations and analysis found within provide helpful information that the FDA can utilize in its analysis of cannabinoid product manufacturing, safety testing, packaging, and labeling. With one voice, the National Cannabis Industry Association seeks to work collaboratively with the federal government to improve the health of consumers, the business community, and society at large. We believe that our past work, as well as these comments submitted for the public record, aid that process of continual improvement. The NCIA seeks to establish a strong working relationship between the federal government's regulatory agencies and a vibrant young industry of entrepreneurs who are excited to embrace the new federal standards that come with legal recognition.

The NCIA Policy Council published *Cannabis Testing Policy: Recommendations for More Thoughtful and Consistent Regulations* in July 2018. The NCIA published this report with the intent of helping guide state and federal policymakers as they establish standards for cannabis testing and analysis. The report provides 16 different recommendations to consider for an effective and efficient third-party cannabis testing program. These recommendations cover issues including but not limited to the creation of a cannabis laboratory advisory commission composed of experts and other stakeholders; the types of policy issues that should be covered in statutes, regulations, and policy publications; laboratory accreditation; testing lab ownership; batch and sampling policy; required potency and contaminant testing; testing requirements at various stages along the production supply chain; educational requirements for select laboratory staff; product remediation; and testing of cannabis from unlicensed sources.

The NCIA Policy Council's testing research determined that the first and most important component of establishing a well-regulated cannabis testing program starts with the creation of an ongoing policy consulting stakeholder working group. This group, the Cannabis Laboratory Advisory Commission (CLAC), would be composed of experts in public health, laboratory accreditation, cannabis, and testing science as well as operators and government officials. The core role of CLAC would be to bridge the informational gap between cannabis testing laboratories and their regulators. Cannabis testing is both new and complex, so CLAC would work collaboratively to ensure that all regulations and policies are operational, effective, and efficient. In addition, CLAC would draft policy papers and position statements that direct the activities of laboratories but that either are too detailed or require too frequent modification to be placed in law or regulation. This brings us to the second key issue of cannabis testing. The detailed nature of testing policy and continual advancements in the field of analytical testing mean that regulators must maximize flexibility and responsiveness. Issues such as the permissible levels of residual solvent contaminants and processes for required sampling should be reserved for policy guidance where changes can be made based on new scientific findings outside of normal rulemaking processes. If such a system was established at the federal level, this guidance would then be enforced by state regulators in an orderly fashion to ensure testing facilities and industry participants understood the new requirements and had ample time to come into full compliance.

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Cannabis businesses are still maturing, and at this stage the NCIA Policy Council believes it is important that cannabis testing remain independent. All analyses used to certify products as ready for commercial release should be performed by laboratories audited to internationally recognized standards. To the greatest extent possible, these third-party laboratories must have their processes and results continually updated and validated to ensure that accuracy is maintained. In this area of policy, existing internationally recognized standards applicable to analytical testing facilities generally, such as ISO/IEC 17025 and The NELAC Institute standards, can be applied to licensed cannabis laboratories. Accreditation bodies, such as the American Association for Laboratory Accreditation and the ANSI-ASQ National Accreditation Board, already certify cannabis testing laboratories to ISO/IEC standards. While many other existing industries do not require independent analytical testing for each product batch, this type of public health evaluation is important to reassure the public that cannabis on the regulated market is accurately labeled and free of harmful contaminants. Sample collection and preparation must also be performed by an unbiased third party. If manufacturers or cultivators are permitted to select their own samples for testing, there are risks that the samples collected and prepared would not be truly representative of the production batch. Without representative samples, contaminated or otherwise adulterated cannabis products could be sold to the public. To ensure that test results are accurate, all third-party cannabis testing laboratories must participate in state-mandated proficiency testing programs. These programs require state laboratories to test known samples in order to compare the results and identify testing laboratories that may need additional process validation. Without continual state auditing and testing of testing facilities, some operators could seek out labs that would provide them with the most desirable results rather than those that are truly accurate.

When considering how to test cannabis products for health and safety, it is essential to look to the procedures in place for other consumer products. It is not feasible or realistic to test cannabis for every single potentially hazardous compound. Instead, contaminant testing must be targeted to the most likely forms of cannabis contamination that pose the greatest potential health hazards. Typically, states have adopted mandatory contaminant testing in cannabis programs centered around screening for hazardous microbials, heavy metals, residual hydrocarbon solvents used during extraction, foreign particulate matter, and mold and yeasts. As the science and cannabis markets have evolved, certain states have adopted additional requirements for water activity, mycotoxins, pesticide residuals, and cultivation chemicals. These regulatory developments are largely guided by publications from the American Herbal Pharmacopoeia and the United States Pharmacopoeia detailing specific lists of contaminants that should be screened. Similarly, required potency testing should target the cannabinoids and other potentially intoxicating substances that are most likely to appear in cannabis. Although THC is the most common and well-studied cannabinoid, it is just one of dozens of different active chemical constituents in the cannabis plant. While other minor cannabinoids and terpenes may have pharmacological effects and act synergistically, most exist in minute and often undetectable levels. At a minimum, most states require the testing and labeling of total THC and CBD. Certain states, such as Alaska, Connecticut, and Maryland, seek to identify a wider array of active constituents and require testing for the cannabinoids cannabidiol (CBD) and cannabigerol (CBG), as well as terpenes commonly found in the cannabis plant. Instead of testing for every possible cannabinoid, the NCIA Policy Council believes that state-mandated cannabis potency testing requirements should focus on protecting public health by analyzing psychoactive THC

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levels and ensuring accurate testing and labeling of all other marketed cannabinoids and terpenes.

Cannabis testing provides important public health and safety benefits to consumers and society at large. But it also increases the incremental costs of cannabis products. During this initial phase of cannabis implementation and development, increased costs could push price-conscious consumers back into the illicit market. As such, it is vital that policymakers consider ways to ensure that testing is performed efficiently as well as effectively. The frequency of mandated third-party testing is the most significant driver of testing costs. To reduce the risk of improper sampling error, some states restrict the production lot size of cannabis flower and cannabis products. This means that no matter how a business structures production, cannabis products may still have to be divided into separate five- to ten-pound lots for testing. This increases costs and does not conform to established testing and sampling procedures in other industries. Instead, cultivators and manufacturers should be permitted to produce production batches of any size, with independent samplers then selecting the necessary number of sample increments to ensure that the test sample is representative of the entire batch. In addition to batch size, policymakers should carefully consider when in the production cycle a cannabis product should be tested. In states like Colorado, edible products are tested for potency and contaminants multiple times: when the cannabis flower is harvested, when the oil is extracted, and when the final infused product is produced. If these activities occur in the same vertically integrated facility, additional stages of required testing just increase costs without advancing public health and safety. Instead, third-party testing of cannabis products should be required only after the product is manufactured in its final form, prior to being transferred to retail stores. Businesses may assess their input ingredients to ensure that potency is accurate and contaminants are not present, but the government's role of preventing unsafe products from reaching consumers is satisfied as long as cannabis in its final form is tested.

Although cannabis has been consumed by humans for thousands of years, most cannabis produced over the last century was grown and processed in an era of prohibition without any safety standards for labeling and packaging. Cannabis was sold in plastic baggies with no labels and just a mention of a strain name. Only in the past decade have consumers begun to see carefully packaged and labeled cannabis products with relevant information on potency and ingredients. Since medical and adult-use cannabis products are regulated by the states, and cannabis is not currently permitted at the federal level, all labeling guidance must come from state health agencies. To assist states in this endeavor, the NCIA republished *Cannabis Packaging and Labeling: Recommendations for Sensible and Consistent Regulations Across States and Nations* in February 2019. This comprehensive analysis of cannabis labeling and packaging policy was guided by the following five objectives: (1) to ensure that cannabis packaging and labeling regulations protect public and consumer health and safety; (2) to align state cannabis packaging and labeling regulations with federal laws and regulations for packaging and labeling of products with shared characteristics (e.g., food products, drugs, dietary supplements, cosmetics, alcoholic beverages, and tobacco products), when appropriate; (3) to ensure that cannabis packaging and labeling regulations have a sound legal and empirical basis; (4) to encourage uniformity in state cannabis packaging and labeling regulations; and (5) to identify packaging and labeling requirements for cannabis that are effective and operable, while recommending the elimination of those that are not. To best assist state and federal policymakers

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in their work developing new cannabis product regulations, the paper is structured into 20 different policy recommendations across both labeling and packaging and concludes with a full set of model regulations.

Product labels are intended to convey important safety and marketing information to consumers. For non-cannabis consumable items, this means informing consumers of product type, brand, ingredients, and nutritional facts. Because of their risks, OTC drug products include additional labeling information for active ingredients and consumer warnings. Cannabis products, which often contain active drug components along with other edible ingredients, must incorporate labeling policies from both the packaged goods and OTC pharmaceutical industries. But it is equally important that labels do not get overcrowded with too much text and information. An overwhelmingly dense label in a tiny font that consumers end up not reading provides only slightly more helpful information than no label at all. To avoid presenting labels as a “wall of text,” rules should mandate a minimum text size while balancing the number of warning statements with other requirements. The most important information should be clear and easy to see. The NCIA Policy Council recommends including a “cannabis facts panel,” similar to an active ingredients label on an OTC medication, that provides information on the percentage of effective THC and all other marketed cannabinoids. Potency should be presented as a percentage if the product is intended to be smoked or vaporized and by milligrams if the product is intended to be orally or topically consumed. In addition, edible products must—like all other food products—contain information on ingredients, potential allergens, and nutrition facts. To ensure that consumers see and read important warning statements, the font should be enlarged, and the number of statements should be limited to only those essential to public health and safety. Small or otherwise unique product packages should be permitted to fulfill certain labeling requirements with an attached tag, peel-back label, or fold-out accordion label. The NCIA suggests the following warning statements on labels for the specified product types:

For all cannabis products:

*“KEEP OUT OF REACH OF CHILDREN AND PETS.” “This product may be unlawful outside of the State of [insert state].”*

For all adult-use cannabis products:

*“For use only by adults twenty-one years of age or older.”*

For all medical cannabis products:

*“For medical use only.”*

For psychoactive cannabis products:

*“This product may have intoxicating effects. Do not drive or operate heavy machinery while under the influence of cannabis.”*

For all ingestible infused products and activated concentrates intended to be used in cooking, eaten, or otherwise swallowed and digested:

*“Activation times vary but may be up to two (2) hours after this product is eaten or swallowed.” (or an alternative statement supported by data from an activation time study and approved by the Department)*

To alert consumers, as well as young children, that cannabis products are restricted to adults, the federal government should consider adopting a universal warning symbol. Currently, many state cannabis programs require a specialized symbol, often a variant of a stop or yield sign with a

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cannabis leaf or the letters THC, which indicate that the product contains cannabis. While these different state symbols are helpful, it would be more effective if the federal government adopted a universal nationwide standard and funded an accompanying public awareness campaign with relevant information about the symbol and warnings on cannabis products.

Important child-resistant safety measures are already required in medical and adult-use cannabis programs across the country. While cannabis product labeling is designed to display relevant information to adult consumers, cannabis packaging is designed to keep out young kids. Most state cannabis laws require products to be packaged in child-resistant containers, just like many pharmaceuticals, in accordance with the Poison Prevention Packaging Act of 1970. Federal special packaging standards and test methods have been in place for decades and can easily be applied to cannabis products. The NCIA recommends defining child-resistant packaging to conform with the federal test protocol for “special packaging” established in 16 C.F.R. 1700.20, as amended in 1995. Following the special packaging specifications set forth in 16 C.F.R. 1700.15, we further recommend requiring that every multi-unit ingestible or transdermal cannabis-infused product be dispensed in packaging that is resealable and maintains its child-resistant effectiveness for at least the number of consumable units in the product. To accommodate the elderly or otherwise handicapped persons, cannabis businesses should also be permitted to provide a limited number of non-child-resistant packages as long as there is a conspicuous warning stating, “This package is for households without young children.”

Cannabis product packaging, particularly edible products, must not be labeled or designed in a way that could be attractive to children. Most legal cannabis states require edible cannabis products to be placed in opaque packaging. NCIA supports this policy for two primary reasons. First, public health researchers have found evidence that opaque packaging makes products less appealing to adolescents and could help limit ingestion of a package’s contents by children under the age of seven. Second, at the federal level, the U.S. Pharmacopeia requires light-resistant containers to protect certain drugs from the effects of light, which includes opaque containers and translucent containers affixed with an opaque covering. As such, opaque packaging is recommended for all edible product sold at retail. With the application of uniform standards based in science and public health, cannabis products of all types can be manufactured and sold to adults while limiting the attractiveness and ease of access for minors.

## **Conclusion**

On behalf of the National Cannabis Industry Association, and in response to the U.S. Food and Drug Administration’s request for comments on Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds, published in the April 3, 2019 edition of the Federal Register, we are pleased to submit these public comments.

Given the substantial interest in this topic and the need for regulations and standardization throughout the industry, the NCIA hopes that the FDA will act with due deliberation and speed in effectuating a regulatory regime that works for the industry and regulators alike. We stand ready to work with the FDA and any other interested parties to effectuate a regulatory regime that protects consumers, entrepreneurs, and federal, state, and local government entities.

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