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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Comment on Proposed Rule Regarding Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds (Docket No. FDA-2019-N-1482)**

The Center for Science in the Public Interest (CSPI) respectfully submits the following comments on the Food and Drug Administration's (FDA's) Request for Comments Regarding Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds.

Legalization or decriminalization of cannabis is occurring at the state level, producing a legal patchwork with inadequate policies and funding to protect consumers. Cannabinoids and the risks they may pose are poorly understood. Nonetheless, cannabis-derived substances, mostly cannabidiol (CBD), may be found today in hundreds of supplements, foods, and other products. This exploding marketplace for consumer goods is well out in front of federal law, which (despite its myriad flaws) historically provides the most robust assurance of safety and quality in food and drugs. Decriminalization addresses a host of problematic aspects of prohibition, including long-standing patterns of racial discrimination in the prosecution of marijuana-related criminal offenses. But current state legalization approaches, combined with lack of clarity over the Federal role, fail to provide appropriate levels of consumer protections.

It is critical that FDA assert its authority on behalf of consumers to ensure that products are safe, accurately labeled, and free of adulterants and contaminants, and that consumers are aware of any relevant risks. To do so will require that the agency articulate a long-term program to align the state laws that legalize these products with applicable federal health and safety protections, as we describe below.

***Executive Summary: FDA Should Assert its Role to Protect the Health and Safety of Consumers of Cannabis***

As FDA notes in its request for comments, under the auspices of state or local law, 33 states and Washington, D.C., now allow so-called "medical" use of marijuana, and 14 additional states have created a "medical" status to allow sales of products containing cannabidiol (CBD).[1] Ten

states and Washington, D.C., have legalized recreational use of marijuana and 13 additional states have decriminalized recreational marijuana possession.[2]

At the Federal level, the Agriculture Improvement Act of 2018 (the "Farm Bill"), de-scheduled hemp, meaning that cannabis plants and derivatives with no more than 0.3% tetrahydrocannabinol (THC) on a dry weight basis are no longer controlled substances.[3] The same law specifically preserved FDA's authority to regulate cannabis and cannabis-derived compounds.[4]

The changes in legal status have produced a rapidly exploding consumer cannabis market. The National Cannabis Industry Association formed in 2010 and now represents "nearly 2,000 member-businesses and tens-of-thousands of cannabis professionals" manufacturing both CBD and THC-containing products.[5] National retail chains including CVS, Walgreens, Rite Aid, Vitamin Shoppe, GNC, and Kroger have begun selling CBD products, and companies like Organa Brands and Zoots sell THC products in multiple states. National consumer sales of CBD products totaled $512.7 million in 2018, and "legal" sales of marijuana were nearly $10 billion in 2018.[6] Sales of cannabis edibles reached over $1 billion in the same year. [7] Tinctures, capsules, and edibles make up over 60 percent of the CBD market.[8]

Even prior to these actions, marijuana was widely used by consumers and was the most commonly used illicit substance. In 2016, an estimated 24 million people age 12 and over in the United States used marijuana in the past month.[9] Moving so quickly from decriminalization to a large marketplace for consumer goods has led, over a period of just a few years, to an incomplete patchwork of state laws and rules. While states are generally making an effort to implement consumer protections, the lack of a uniform set of best practices, at both state and federal levels, is putting consumers at needless risk.

The marijuana marketplace is rife with products that may appeal to children; are contaminated, adulterated, or mislabeled; are highly potent; as well as products that make misleading claims about content and efficacy. Many products lack appropriate warning statements, packaging and child proofing. In such an environment, consumers cannot be assured of product content, much less make informed decisions about whether to use the products.

Edibles pose particular risks due to their delayed, variable, and long-lasting effects, as well as the potential for both intentional and unintentional consumption by children. It is important that children be protected from unintentional consumption; that older children be discouraged from use of these products; and that everyone, including vulnerable populations such as pregnant women, be informed of any risks that may apply.

Even as the number of products explodes, the medical benefits of cannabis remain poorly understood and the risks of use poorly characterized. According to a 2017 report by the National Academies of Sciences, Engineering, and Medicine, there is conclusive or substantial evidence that cannabinoids are effective for only three therapeutic uses.[10] Moreover, the FDA has approved only four drugs for specific medical conditions—Epidiolex, Marinol, Syndros, and Cesamet—which contain compounds found in cannabis or synthetic ingredients that mimic such compounds.[11] These drugs are clinically indicated to treat seizures associated with Lennox-

Gastaut syndrome and Dravet syndrome in patients age 2 years and older (Epidiolex) and to counteract the nausea and vomiting associated with chemotherapy and treat anorexia associated with weight loss in AIDS patients (Marinol, Syndros, Cesamet).

Nevertheless, dozens of ailments are recognized by state medical marijuana programs, and many states have policies that do not limit access to medical marijuana to patients with provable qualifying ailments but rather allow patients to access medical cannabis whenever their physician deems necessary.[12]

Products containing cannabis are already taking a toll on public health. At a large urban academic hospital in Colorado, there were 2,567 emergency department visits at least partially attributable to cannabis from 2012 to 2016, with the number of these visits increasing each year.[13] In Washington state, the number of cannabis exposures reported to one poison control center increased by 158 percent, from 146 in 2011 to 378 in 2017 (recreational use became legal in the state in December 2012).[14] Forty-three percent of these exposures involved edibles, and another 17 percent involved concentrates.

The federal legal status of cannabis, alongside the lack of research and consumer understanding, means that, in practice, consumers are being exposed to a wide range of harms that could be mitigated, at least in part, by appropriate regulations. As states and localities historically have had only a supportive role in assuring food and drug safety, the lack of a federal program to assure that products are as safe as possible, are not mislabeled or adulterated, and are consumed only by informed consumers, is regrettable.

In some respects, tobacco offers a public health-oriented model upon which the regulation of cannabis could be built. The product could be legal, but its harm should be mitigated insofar as feasible by law and policy.[15] As with tobacco, community education, packaging, warnings, and other rules can be significant tools in combatting harm and reducing the costs to the public. Driving under the influence of cannabis also remains a specific problem that will require highly specific law enforcement and public education solutions. In short, cannabis policy must be grounded in public health, not profitability, and use of cannabis by consumers should be as safe as possible.

Many uses of cannabis intersect with a distinct area of federal law, whether food, dietary supplements, or drugs. FDA should consider each product category a separate opportunity to design policy that protects consumers and does not permanently distort FDA's general authorities. In addition, FDA should apply a risk-based framework that distinguishes higher risk uses of cannabis from lower risk applications (*i.e.*, different rules could apply to psycho-active cannabinoids, such as THC, than to non-psycho-active cannabinoids, such as CBD).

Current FDA policy is to wield the so-called "exclusion rule" like a rhetorical sword. This rule provides that any substance that is the active ingredient in an approved drug may not be allowed as an additive in food or an ingredient in a dietary supplement.[16] It is a sound idea generally.

However, there are more than 104 cannabinoids in cannabis and, as FDA concedes in its "Q&A," the exclusion rule currently encompasses only CBD and THC, as these are the only cannabinoids

that are active ingredients in approved drugs.[17] Moreover, application of the exclusion rule would create only a single pathway—drug approval—for CBD and THC, which, as a practical matter, would mean that FDA would continue to fail to assert meaningful jurisdiction over the safety of other uses legalized by states or local governments or the presence of cannabinoids other than those for which it has granted approval.

Under the law, the FDA may waive the exclusion rule at the agency's discretion, after issuing a regulation following notice and comment and finding that the article would be lawful under the Federal Food, Drug, and Cosmetic Act.[18] Such a waiver, then, must be consistent with the broad purposes of the FDA to assure and improve public health and safety. If issued, the waiver should be designed to reconcile conflicts between state and federal law in the service of health. It must also be the case that FDA has or will establish a network of regulations, guidance, and enforcement priorities that are equal to these tasks.

As a practical matter, development of such a waiver would require FDA to develop a concrete, public-facing program to address each category of cannabis product within its jurisdiction, to take steps to specifically mitigate their risks, and to enforce norms that, over time, bring these state and local programs into alignment with applicable federal laws supporting consumer health and safety.

FDA lacks adequate legal authority to assure consumer safety, and the consistency or quality of products containing cannabis that may be sold as dietary supplements. The agency should continue to assert that such products are illegal under federal law and should ask Congress for additional authority to regulate supplements generally, including new authorities pertaining specifically to cannabis.

**Addressing Safety Concerns Pertaining to Cannabis Products**

*Evidence Concerning Known and Potential Risks of Cannabis Use*

In many ways, we lack a definitive picture of public health concerns related to cannabis products. The National Academies of Sciences, Engineering, and Medicine (NASEM) summarized the known health effects of cannabis and cannabinoids in a 2017 report.[19] The panel found "substantial evidence" of the following adverse health effects:

- Worsened respiratory symptoms, including more frequent chronic bronchitis episodes (long-term cannabis smoking);
- Increased risk of motor vehicle crashes (cannabis use);
- Lower birth weight of the offspring (cannabis smoking in pregnancy); and
- Development of schizophrenia or other psychoses, with the highest risk among the most frequent users (cannabis use).

But much else remains unknown. NASEM recommended a wide-ranging research agenda to "address current research gaps, highlighting the need for a national cannabis research agenda that includes clinical and observational research, health policy and health economics research, and public health and public safety research."

*Serious Safety Concerns Related to Cannabis Products*

Adulteration and contamination (including pathogens, heavy metals and pesticides) are problems throughout the cannabis marketplace. When the plant is extracted or concentrated, an Oregon state audit notes, it "may present a greater risk as any contaminants will become concentrated during processing."[20]

As the state of Oregon's report on the oversight of cannabis safety by the state noted, "marijuana is efficient at absorbing and storing heavy metals and other pollutants found in soil and water."[21] Indeed, hemp plants are so efficient in absorbing contaminants (called "phytoextraction") that they have been used to clean soil, including soil following the nuclear reaction at Chernobyl, and their use is anticipated to assist in cleaning industrial waste sites.[22] For this reason, the Association of Public Health Laboratories published a report in 2016 recommending testing for heavy metals, solvents, pesticides and microbiological contaminants in marijuana.[23]

Major safety hazards related to cannabis edibles, specifically, include variable levels of THC, CBD, and other cannabinoids; aflatoxins; chemical residues; high levels of pesticide residues; heavy metals; and dangerous pathogens.[24] The same concerns also apply more generally to all cannabis products. For example:

- Product testing in Massachusetts revealed lead levels in cannabis products up to 96 times higher than the legal lead limit for marijuana in the state.[25]
- Testing in Washington state found that more than 12 percent of marijuana products contained mold, Salmonella, or E. Coli.[26]
- The California Bureau of Cannabis Control recently reported that 514 out of 10,695 products sampled, or 5 percent, were rejected for unacceptable levels of pesticides or bacteria.[27]
- A 2015 investigation by The Oregonian reported that independent labs the paper commissioned to conduct blind tests found 14 pesticides on 10 marijuana extracts. Most were considered potential carcinogens and either exceeded permissible levels under state law or were excluded from pesticide regulation.[28]
- Samples tested by the media organization NBC4, the NBC News affiliate in Los Angeles, in 2017 found evidence of widespread pesticide contamination, with 41 out of 44 samples purchased in California dispensaries testing positive for pesticides at levels high enough to be banned from sale in some states that regulate the use of pesticides in marijuana products.[29] The study found that 93% of the products purchased in retail shops and then submitted for testing had unacceptably high levels of pesticide contamination. California has since introduced testing requirements covering pesticides, solvents, heavy metals, and microbiological contaminants.[30]
- Myclobutinal, a pesticide that converts into highly toxic hydrogen cyanide gas upon combustion, was notably present in several of the California shelf tests. Myclobutinal has also been detected in hundreds of pesticide tests in Oregon, and above the action level in many cases."[31]
- Ingredients not listed on product labels, including synthetic cannabinoids, have been identified in cannabis products.[32] Nine product samples purchased by investigators in Utah, labeled as CBD products, contained a synthetic cannabinoid, but no CBD.[33]

- In 2016, in a single recall, 100,000 packages of marijuana edibles were removed from shelves due to concerns that they may contain two pesticides (imidacloprid and myclobutanil) prohibited in marijuana production in Colorado.[34]
- State and local health authorities cite concerns about the potential for presence of dangerous pathogens, especially in plant-infused oils and perishable food products.[35] One concern is the potential for bacteria that can lead to botulism due to lack of refrigeration. In 2014, a Colorado manufacturer, Mile High Distributing, was sent a cease-and-desist order and told to recall infused olive oil and liquid THC drops stored at room temperature.[36] Washington is currently the only state that limits sales of edibles to shelf-stable products.[37]

*Mislabeling, High Potency, and Risks of Overconsumption of Cannabis Products*

Mislabeling is also a widespread issue. The levels of THC, CBD, and other cannabinoids in cannabis products frequently vary significantly from the levels declared on their labels. Testing of cannabis products has identified widespread misbranding, including the presence of higher levels of THC in CBD products than are permitted by law:

- Tests of 84 CBD products available online in 2016 found that 1 in 4 had CBD levels significantly higher than indicated on the label. Overall, 58 of the 84 products (69%) were inaccurately labeled, with higher or lower CBD concentrations. Moreover, THC was detected at levels over 0.3% (with levels exceeding 6 mg/mL in one instance) in 18 of the 84 samples tested; cannabidiolic acid was detected in 13 of the 84 samples; and cannabigerol in 2 of the 84 samples.[38]
- A study testing 75 products from 47 brands obtained in Seattle, Los Angeles, and San Francisco found that 17 percent were accurately labeled, 23 percent were under-labeled, and 60 percent were over-labeled with regard to THC levels. In addition, 44 products (59%) had CBD but only 13 products (17%) were labeled for CBD.[39] Four products were under-labeled for CBD and nine were over-labeled for CBD.[40]
- A 2018 investigation of six of the largest cannabis testing labs in Washington state found systematic differences in results obtained by different testing facilities, with some labs consistently reporting higher or lower levels of cannabinoids than others. Results suggest a trend of "cannabinoid inflation" by labs, as well as differences in capacity of labs to detect low-level cannabinoids.[41]

There is tremendous variability in the effects of cannabis consumption upon individuals, including the effects of particular doses.[42] Occasional users report feeling "high" after consuming only 2-3 mg of THC.[43] Inhalation of cannabis containing 10 mg of THC can produce impairment of cognitive and psychomotor ability.[44]

Cannabis producers appear to be breeding plants for higher THC content, as THC potency in marijuana is on the rise. An analysis of 36,681 samples of cannabis (37,606 cannabis, 814 hashish, and 261 hash oil) obtained by the Federal Drug Enforcement Administration between 1995 and 2014 found that their average potency has consistently increased over time, from 4 percent in THC 1995 to 12 percent THC in 2014.[45] In a 2011 report to the European Monitoring Centre for Drugs and Drug Addiction, an expert committee advised that the Netherlands move

cannabis containing more than 15 percent THC to the list of the most dangerous drugs (Schedule I).[46] Recommendations from the Institute of Economic Affairs to the UK government also recommend a 15 percent limit on THC in legal cannabis.[47]

Limiting levels of THC per serving in edibles is consistent with industry advice, although states have set higher serving sizes for THC regardless. The Council on Responsible Cannabis Regulation, a legalization advocacy group, ran a campaign urging first-time users to ingest no more than 5 mg of THC in a sitting,[48] which is half a serving size under Colorado and Washington laws. This recommendation is embraced by the Marijuana Policy Project, which runs a campaign titled "Consume Responsibly" that urges inexperienced users to start with 5 mg of THC, noting that the effects of more have proved too powerful for novice users and some users with smaller body types.[49]

But food and dietary supplement products presently available for sale may contain levels of THC that far exceed these amounts (see Appendix B for examples). Korova edibles sells a 2-ounce brownie containing an entire gram of THC.[50] The product claims to contain 100 servings, but it is hard to imagine most consumers restricting themselves to eating 1 one-hundredth of a standard-sized brownie to achieve this dose. Enjoyable Edibles also sells a 1-gram THC brownie, called the "Blackout Brownie," which contains 20 servings—that is, 50 milligrams of THC per serving, still well in excess of even industry recommendations.[51]

Clinical trials for Epidiolex revealed that CBD doses of 10 to 20 milligrams per kilogram of body weight per day create a potential for liver injury.[52] The frequency of transaminase elevations in the controlled trials and in the Expanded Access Program was 8 percent in the 10 mg/kg/day CBD group, 16 percent in the 20 mg/kg/day CBD group, and 3 percent in the placebo group. Some of these events were serious or severe, but there were no events of liver failure or death related to liver injury, and all transaminase elevations were resolved (some during continued CBD treatment).

High potency CBD products, including products marketed for children, are currently available for sale. The company Hemp Bombs sells teddy bear-shaped CBD gummies with up to 25 mg CBD per gummy and up to 1500 mg CBD per unit of sale (see Appendix B).[53] The product's packaging bears no warning of liver injury and does not warn about use by children. A 25-kg child may experience elevated transaminases after consuming 10 of these gummies per day.

FDA should consider CBD products containing more than a specified amount of CBD per serving and per package or unit of sale (to be decided by the agency based on the available evidence of risk to public health) to be high risk and target enforcement actions at manufacturers of high potency CBD products, especially when individual servings are not clearly demarcated. Another element of enforcement should be labeling, including when the product's labeling of THC-containing products does not include information about delayed effects.

Several state governments are working to address these safety risks through state testing programs and regulation.[54] Yet these programs often struggle with resource constraints and lack of technical expertise to identify and address the many safety risks presented by these products. For example, while Washington State requires limited third-party testing for potency and

contaminants, a number of complaints and allegations were lodged against third party testing labs for publishing suspiciously favorable results, a sign of potential fraud.[55] A recent Oregon state audit noted concerns about "lab shopping," which occurs "when clients jump from lab to lab to seeking desired results."[56]

The same Oregon audit makes clear that enormous gaps in testing, audits, and inspections in the state persist and pose serious risks to consumers.[57] The report noted that there is a lack of validated testing protocols, noting that "unlike other kinds of environmental lab testing there is a general lack of guidance available to these labs; no standard methodologies are in place for testing, for example."[58] As of October 2018, just 4 of the state's 22 labs were fully accredited for all required tests, so subcontracting is common and regulators are unable to identify discrepancies and problems in reporting to the state.[59] Testing protocols, according to the report, also have multiple vulnerabilities to intentional and unintentional manipulation.[60] The report concluded that:

> Without a mechanism for verifying test results, Oregon's marijuana testing program cannot ensure that test results are reliable and products are safe. Limited authority, inadequate staffing and inefficient process reduce [regulators'] ability to ensure Oregon marijuana labs consistently operate under accreditation standards and industry pressures may affect lab practices and the accuracy of results.[61]

In sum, state regulations are currently inadequate to manage these risks, indicating a need for heightened federal scrutiny. Overall, the lack of appropriate testing standards, validation, certification and audit and inspection programs badly impair state oversight of the industry.

**Risks to Children and Youth Warrant Priority Enforcement for FDA**

The long-term risks associated with adolescent cannabis use are well-documented, but not well understood. Such risks include negative impacts on neurocognitive functioning and brain development and increased risk for schizophrenia in adulthood.[62]

Many cannabis products may appeal to children, especially "edibles" in the form of candy, baked goods, and snack foods. These and other products have particular appeal to children when their packaging includes bright colors, cartoons, and images of candy or fruit. Alaska and Colorado are examples of state with regulations that try to protect children by prohibiting some forms of child-targeted packaging.[63]

In addition, FDA should parallel FDA's rules for cigarettes and bar flavorings in smoked or vaped cannabis. Flavored products with a wide variety of flavors are a key tool for attracting young smokers to tobacco and e-cigarettes.[64] Most adolescent tobacco and e-cigarette users currently use and initiated with flavored products.[65] Disguising unpleasant tastes with flavors to attract young users is a tobacco industry strategy that could easily repeat for manufactured cannabis products absent strong regulations.

Children are also at risk of acute poisoning from exposure to cannabis. According to Children's Hospital Colorado, "[t]he most common overdose incidents in children occur when the drug has been combined with food in an 'edible' form of marijuana."[66]

Cannabis-related incidents reported to national poison control centers are increasingly common in states where the drug has been decriminalized. Even prior to recreational legalization in Washington and Colorado, a review of data from the American Association of Poison Control Centers National Poison Data System found there were 985 unintentional marijuana exposures reported among children aged 9 and under from 2005 to 2011, the period before the first states (Colorado and Washington) legalized recreational marijuana in 2012.[67] And exposures are on the rise—the call rate in states with decriminalization over the same period increased by an average of 30 percent per year but did not change in nonlegal states (see Figure 1).[68]

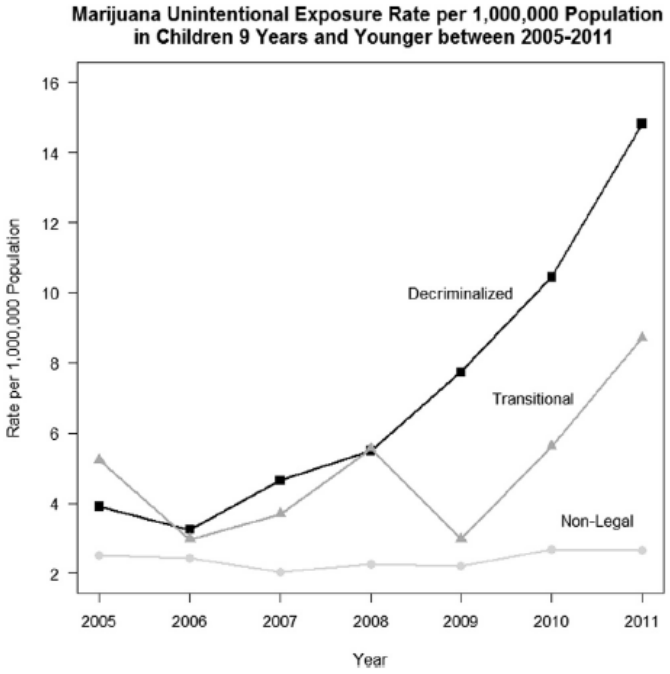



Figure 1. Comparison of unintentional marijuana exposure rates between nonlegal, transitional, and decriminalized states
Source: Wang GS, et al. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States.

Another study found that between 2000 and 2013, there was a shocking 609 percent increase in accidental pediatric exposures and ingestion was the most common route of reported unintentional pediatric exposure, accounting for 78 percent of all incidents (see Figure 2).[69]

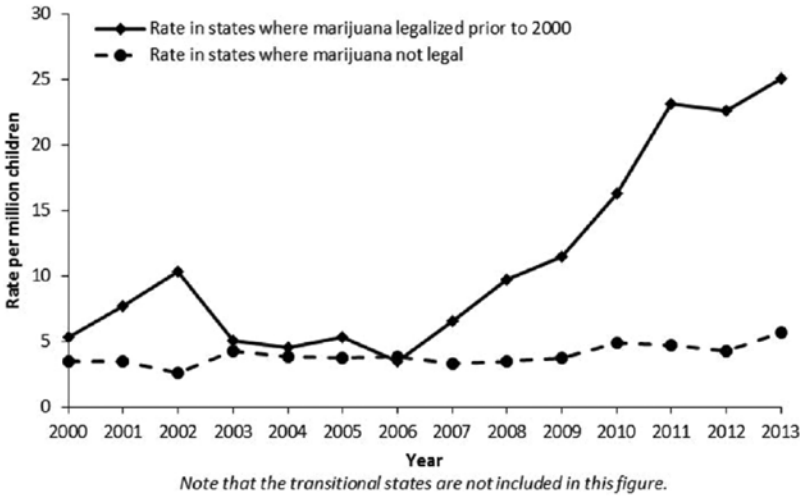



Figure 2. Annual rate of marijuana exposures among children younger than 6 years by marijuana legalization status of state (National Poison Data System, 2000-2013)
Source: Onders B, et al. Marijuana exposure among children younger than six years in the United States.

More recently, in the years following the 2012 legalization of recreational cannabis in Washington state, the number of cannabis exposures reported to the state's single poison control center increased by 158 percent, from 146 in 2011 to 378 in 2017, and the number of cannabis exposures for children age 0 to 5 increased almost sevenfold, from about 12 exposures in 2011 to 82 exposures in 2017 (see Figure 3).[70] Of an unknown number of those cases followed to a known medical outcome, 23% of the individuals exposed developed moderate or life-threatening symptoms.[71] Symptoms reported in association with pediatric cannabis exposure include those as serious as seizure, respiratory depression, and coma, but no deaths.[72]

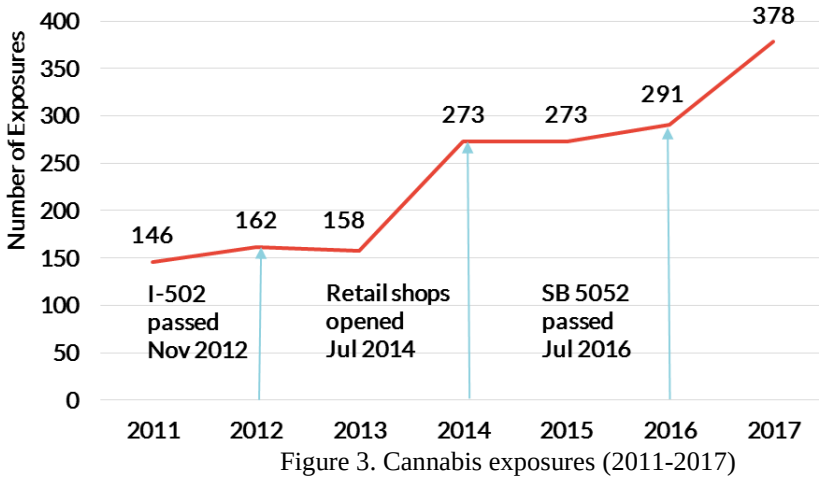



Figure 3. Cannabis exposures (2011-2017)
Source: Washington Poison Control Center. Annual Toxic Trend Report: Cannabis. 2017.

Cannabis may contain a combination of CBD, THC, and other cannabinoids in various proportions. While the risks attributable to THC, a psychoactive compound, likely exceed those attributable to CBD, a non-psychoactive compound, there is insufficient data to be able to reliably characterize cannabinoid-specific risks, particularly for young children.[73] Given the hazards of both chronic and acute exposure to cannabis in children and adolescents, CBD and THC products that may appeal to children should be considered a higher-risk product category subject to FDA's enforcement priorities. This should include any food or dietary supplement products or packages that:

- are shaped like humans, animals, or fruits;[74]
- closely resemble a familiar food or drink item, including candy;[75]
- bear images of cartoons, animals, fruits, cookies, candy, or other sweets;
- are in forms like baked goods or other foods typically marketed to youth or sent to school, such as Rice Krispies treats, cupcakes, granola bars, and animal crackers, that may be easily mistaken by children for non-cannabis products; or
- lack opaque, resealable, child-proof packaging for each individual serving.

Examples of products that violate one or more of these restrictions can be found in Appendix A. These products would be likely to appeal to children, to whom other similar food products such as fruit snacks, candy, and cookies are regularly marketed. Labeling alone would be insufficient to counteract the influence of packaging that portrays these products as delicious and fun. The best way to prevent child exposure to cannabis-containing products is to limit their appeal to children.

**Edibles Pose Unique Risks to All Consumers**

Despite their clear illegality under federal food law, sales of cannabis-containing edibles are projected to reach $4.1 billion by 2022.[76] Edibles are highly profitable and can account for up to 60% of a dispensary's profits.[77] Since recreational marijuana was legalized in Colorado, sales of edibles grew from $17 million in early 2014 to $53 million in mid-2016.[78]

There is also major ongoing investment in the sector. In December 2017, for example, a private equity firm Privateer Holdings purchased Goodship, which sells edibles in Washington state,[79] and in June 2017, Heineken brand Lagunitas launched "IPA-inspired, THC-infused sparkling water" in California.[80]

Edibles allow marijuana users to ingest THC without the health risks associated with smoking marijuana. Yet THC edibles pose unique risks, and all of these risks are magnified in children. In addition to risks described above from the ingestion of contaminants like heavy metals and pesticides, these include:

- the long duration of their intoxicating effects;
- the significant delay before these effects are felt;
- the similarity to food products in terms of appearance;
- the potential for carrying disease-causing bacteria or pathogens;
- the variability in potency among products and from the amount noted on the label;

- a lack of validated testing for many—if not most—foods; and
- the ease of concealment in school or other settings.

These particular issues are reflected in the data regarding the medical effects of cannabis consumption. A significantly greater proportion (18%) of patients who had been exposed to cannabis as edibles were admitted to emergency departments for acute psychiatric symptoms, such as acute anxiety or acute psychosis, compared with patients exposed to inhalable cannabis (11%), although there may be referral bias.[81]

The delayed effects of THC when consumed in edibles may lead users to consume multiple servings. Individuals who overconsume inadvertently can experience extreme anxiety attacks or psychotic reactions.[82] Medical professionals have previously reported cases of edible cannabis-induced psychosis, and found that "[t]hese patients reported eating the suggested serving size but then consumed over 100 mg of THC after they 'didn't feel anything' and decided to eat multiple portions."[83] This appears to have happened to Levy Thamba, a 19-year-old college student, who ate six servings of a marijuana cookie before jumping to his death off a Denver hotel balcony.[84]

Once edibles are out of their packaging, unintentional consumption is also a risk, because many look exactly like ordinary foods, such as pizza or cookies. Consumers may inadvertently underestimate the risks, because the foods appear innocuous and familiar.

Moreover, some edibles are currently designed to be used in conjunction with stimulants like caffeine, which could mask the sedating effects of cannabis. A recent article notes: "Coma Treats' commercial kitchen churns out chocolate bars, brownies, pepperoni pizzas and a Thin Mint knockoff. The chocolate-dipped 'Wake and Bake' spoon, spiked with 60 to 70 milligrams of THC, is intended to boost the buzz of an ordinary cup of coffee."[85]

Edibles also present specific difficulties for state regulators with respect to quality and potency. The breadth and variation in the types of products makes testing difficult. A list of products from Smart Colorado, a group concerned about the risks of legalization for children, includes a dizzying array of food products, including energy drinks, cherry cola, chai, and a range of coffee drinks.[86] Andy LaFrate, owner of Colorado state-certified marijuana testing lab Charas Scientific, remarked in 2015 that even if a lab develops a standard method that works well for measuring THC in brownies or gummy bears, "next thing we know there is ice cream or pizza we need to deal with."[87]

The risks of inaccurate testing regimes for products and consequent inaccurate labeling are obvious. Adult consumers may experience inconsistent results from consumption of the same or similarly labeled products, leading to unintentional overconsumption. An inaccurate label may increase the risks as it would mean that emergency and medical personnel are unaware of the amount of drug consumed.

*Safety Gaps for Medical Marijuana Put the Most Vulnerable Consumers at the Highest Risk*

According to the 2017 report by the National Academies of Sciences, Engineering, and Medicine, there is currently conclusive or substantial evidence that cannabinoids are effective for

only three therapeutic uses: 1) for the treatment of chronic pain in adults; 2) as antiemetics (anti-nausea drugs) in the treatment of chemotherapy-induced nausea and vomiting; and 3) for improving patient-reported multiple sclerosis spasticity symptoms.[88]
The NASEM report further observed that there are is a fundamental disconnect between the types of research that can be legally conducted under federal law and the products being consumed in states with legalization. The committee noted that:

> [O]nly a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States.[89]

As a result, the committee pointed out that "very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States…more research is needed on the various forms, routes of administration, and combination of cannabinoids."[90]

The FDA has approved four drugs—Epidiolex, Marinol, Syndros, and Cesamet—that contain compounds found in cannabis or synthetic ingredients that mimic such compounds.[91] As noted above, these drugs are clinically indicated to treat seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients age 2 years and older (Epidiolex) and to counteract the nausea and vomiting associated with chemotherapy and treat anorexia associated with weight loss in AIDS patients (Marinol, Syndros, Cesamet).

Nevertheless, dozens of ailments are recognized by state medical marijuana programs, and many states have policies that do not limit access to medical marijuana to patients with provable qualifying ailments. Rather, policies allow patients to access medical cannabis whenever their physician deems necessary.[92]

In addition to being unsupported by evidence, and potentially taking the place of validated medical treatments, some of the "medical" uses being promoted may pose a risk to vulnerable consumers. For example, despite evidence of the risk of lower birth weight described in the NASEM report,[93] a study conducted in Colorado found that 69% of the 400 dispensaries surveyed in a "mystery caller" method were recommending marijuana products to expecting mothers experiencing morning sickness in their first trimester.[94]

The issues of quality and safety described above also apply to medical marijuana. Surprisingly, medical marijuana may be less well-regulated or inspected than recreational marijuana. In Oregon, for example, a January 2019 state audit of gaps in the state's cannabis oversight for both medical and recreational uses found that participation in the program had steeply declined after recreational marijuana was legalized, and that "[m]edical marijuana is […] largely exempt from testing requirements, despite serving patients who may be more vulnerable to contamination than the general public."[95] Inspections by the state of Oregon for medical facilities are also too infrequent. Between January 2017 and September 2018, the state inspected merely 201 (2.9%) of the 6,850 registered medical grow sites in the state.[96] Other gaps may pertain as well: in

Colorado, the state mandates lab testing for a range of contaminants in marijuana products but exempts concentrates.[97]

The Oregon audit explains that "growers in the medical market are exempt from most testing rules and are not required to test usable marijuana product before it is transferred to a medical patient, which could expose patients to contaminants," and that "there are still thousands of patients likely obtaining marijuana directly from medical growers."[98] The inapplicability of pesticide testing rules in the medical marketplace "leaves patients at higher risk for exposure than recreational consumers."[99] The reports notes that "[r]oughly 10% of Oregon's medical marijuana patient community includes children under 18 years of age and seniors over 70."[100] Patients also include individuals who have "conditions such as cancer and HIV that can directly compromise their immune systems."[101]

As a National Environmental Health Association report calling for more robust food safety standards for marijuana succinctly put it, "immunocompromised individuals are the consumers of medical cannabis edibles."[102] In sum, gaps in some states in the standards and oversight for medical marijuana expose the most vulnerable consumers, including children, those with HIV, and the elderly, to the highest risks from contaminants like pesticides, lead and arsenic.

## Suggested General Principles and FDA Actions for Cannabis Products for Food and Drugs

Consumers should be able to make fully informed decisions about the risks and benefits of any consumer product. For any consumer product, consumers have a right to expect that:

1) A product is safe, or for a product well-known to have risks, as safe as possible, to consume as directed;
2) A product does what it claims to do and there is adequate scientific evidence to back up those claims;
3) What is on the label is inside the package and that it is not adulterated with other ingredients, unexpected hazards, or contaminants;
4) Limitations of the product's efficacy are clearly communicated and that safety concerns (such as drug interactions) are also made clear; and
5) If there is a reaction to a product that affects a number of consumers or is serious that both the industry and regulator will act quickly and effectively to protect consumers.

Few of these principles currently pertain to the cannabis marketplace.

### Recommended FDA Actions on Cannabis in Food:

*FDA Should Articulate Clear Enforcement Priorities*

CSPI applauds FDA for recently issuing warning letters to companies illegally selling CBD products that were intended to prevent, diagnose, mitigate, treat, or cure serious diseases, such as cancer.[103] FDA appropriately recognizes that any products bearing claims to prevent, treat, or cure disease—especially serious or life-threatening diseases for which FDA-approved

alternatives are available—should be prioritized as the agency exercises its authority to regulate products containing cannabis and cannabis-derived compounds based on risk to public health.

We encourage FDA to exercise its additional authority by expeditiously developing a public-facing letter, later made into a guidance, making clear that the agency will take action against both CBD- and THC-containing products that pose the greatest public health risks. High-risk products warranting swift enforcement action include:

- products bearing health claims, especially for serious or life-threatening diseases for which FDA-approved alternatives are available, those that raise the possibility of serious side effects, or those that pose a hazard to vulnerable populations, including children and pregnant women;
- products that appeal to or that are marketed for children and youth (see Appendices A and C);
- products containing high doses of either CBD or THC, products with higher concentrations than labeled, CBD products not labeled for THC content but that contain THC; and
- products found to be mislabeled or contaminated, particularly with FDA-approved drugs, synthetic cannabinoids, heavy metals, mold, high levels of pesticide residues, other dangerous chemicals, or pathogens.

FDA should also issue and publicize warning letters to manufacturers of products that make clear that the agency will put these enforcement priorities into practice.

*FDA Should Create a Process for Evaluating the Use of CBD/THC and Other Cannabinoids in Food and Take Interim Steps to Improve Safety*

Under the Federal Food, Drug, and Cosmetic Act, any substance intentionally added to food is a food additive, and is subject to premarket review by FDA, unless it is "generally recognized as safe," or GRAS. The test under federal law for GRAS status is whether there is consensus among knowledgeable experts that a particular substance for a particular use is "reasonably certain to do no harm." Troublingly, under FDA's current final rule for GRAS, companies may also self-determine that a substance is GRAS and choose not to notify FDA or the public of the basis for such a determination or even that such a decision has been made. [104]

While three hemp seed ingredients have been reviewed via FDA's GRAS notification process, FDA's notice makes clear that the agency has not received or approved any other GRAS notifications or food additive petitions for cannabis-derived ingredients.

The GRAS process offers an opportunity for FDA review. As the agency did with partially hydrogenated oils (artificial trans fat), FDA should issue a tentative determination that neither CBD nor THC is GRAS for use in food, and provide the cannabis industry with a specified period of time, such as 2-3 years, for comment and to submit data to the docket before finalizing that determination. As with trans fat, products could continue to be sold during that time.

Such a process might identify doses of particular cannabinoids and/or particular conditions of sale that would be considered GRAS (see more detail below). Over the same period, the industry would be able to develop a pertinent food additive petition for CBD and/or THC requesting approval for specific conditions of use in food.

Such a tentative determination would immediately make clear that FDA is asserting its role and oversight of food and would slow the unregulated advance of these products across the mainstream marketplace. It would also clarify that self-determined GRAS is not an appropriate compliance pathway for such products.

Complicating FDA's assessment is the desirability, from a public health perspective, of preserving an oral administration pathway for cannabis products that diminishes smoking or vaping. FDA should evaluate whether food uses that include a wide range of foods can satisfy food safety, testing validation, and other reasonable conditions of use, and whether some products inherently have appeal to children or risk unintentional consumption. We believe that ingestible forms of cannabis can and should be limited to conditions of use in which potency, quality, testing validation, labeling, packaging and other food safety concerns can be adequately addressed.

*Inspection and Testing and Oversight of Cannabis Edibles*

The process of considering possible conditions of use for CBD and THC in food would allow the industry and states to present any available safety data to the agency and allow FDA to collect all available information on safety, risks, state best practices, contaminants and other matters. During this period, FDA should survey state safety practices, audit state and local inspection regimes, conduct product testing, and analyze the gaps and needs for available data. It should also gather data on risks and evidence on consumer uses, and adjust its determination and enforcement priorities accordingly. Ideas for steps that the agency could take include:

- Testing products for levels of CBD, THC, other ingredients (such as synthetics), pesticides, and contaminants as part of a marketplace monitoring program;
- Designating all food processing facilities manufacturing foods made with cannabis and cannabis-derived compounds as "high risk" and thereby make them subject to routine inspections as well as emergency inspections warranted by safety issues;
- Establishing a rapid response program for issuing injunctions to manufacturers of products involved in serious adverse events;
- Developing a recall program, as FDA has for foods, and test its performance for both supplements and foods;
- Requiring mandatory reporting of both serious and non-serious adverse events by companies; and
- Establishing and strictly enforcing additional public health-based labeling requirements.

As noted above, variable potency, contamination and other manufacturing issues are widespread in the cannabis industry. The FDA should address these problems by making it clear that facilities that manufacture cannabis edibles must register as food manufacturers under 21 U.S.C.

350d. They should also be required to list all the cannabis-containing products they are producing.

State audits document numerous serious deficiencies with current testing, including a lack of validation for tests, lack of certification of labs, lack of credentialing of lab personnel, and lack of funding for inspections and certifications.[105] In addition, regulatory gaps between medical marijuana and recreational systems impact safety.

We urge the FDA to conduct systematic testing of cannabis products, which may be modeled on one of the other quality testing programs the agency has performed for various categories of high-risk products, including raw pet food[106] and contaminated weight loss supplements.[107] We note that in 2015 and 2016, the FDA issued dozens of warning letters for CBD products that the agency had tested and found to contain THC or CBD levels that were above or below the amount of drug stated on the label.[108] A federal testing program is important as it would encourage industry to identify and address manufacturing problems, and would provide important information to consumers about risks associated with these products.

*FDA Should Establish a Process for Considering the of Safety of Cannabis Edibles*

All of the steps described above would bolster FDA's expertise, develop the evidence base for a decision on safety, and help to better protect consumers while the issue is being evaluated. Based on the evidence presented, and whether FDA determines that specific uses or levels of CBD and/or THC can meet the safety standard that applies to food additives, FDA could take one of several actions. It could:

1) approve some uses and levels of CBD and/or THC in foods but set specific conditions of use, including the foods and forms in which it can be used, potency, packaging, limits on contaminants, warnings, and other aspects that pertain to safety, including appeal to children and risks to vulnerable populations; or
2) bar all uses in food of CBD and/or THC.

For example, as part of a condition of use for a food additive for CBD, FDA could establish limits on CBD potency per serving for use, require a standardized symbol for CBD, and require that all CBD products be essentially THC-free. It could also bar uses that may appeal to children, such as candies, gummies, lollipops and the like, and determine packaging and labeling requirements, including for warnings, resealable, child-proof and opaque packaging, and other measures as warranted.

**Recommended FDA Actions on Cannabis in Dietary Supplements:**

FDA lacks adequate legal authority to assure consumer safety, and the consistency or quality of products containing cannabis that may be sold as dietary supplements. The agency should continue to assert that such products are illegal under federal law and should ask Congress for additional authority to regulate supplements generally, including new authorities pertaining specifically to cannabis. In the interim, FDA's enforcement priorities should reflect those articulated for other categories, including food.

For dietary supplements in particular, there are numerous serious gaps in oversight that would impair FDA's ability to appropriately monitor the product marketplace. Disease and treatment claims are rampant both on CBD products, as described above, and more generally on supplements, as our past requests for enforcement by FDA on product claims involving opioid or tobacco cessation make clear.[109]

We agree with Joshua Sharfstein and Pieter Cohen's analysis of the weakness of the opportunities for reforms in a *New England Journal of Medicine* article from June 2019. The article also proposed that Congress should provide additional authority for FDA to regulate CBD in supplements, including mandatory product listing, a stronger safety requirement, and prohibitions on highly concentrated products.[110]

In addition, Congress should provide legislative support for FDA oversight of supplements that includes:

1) warning labels regarding the use of multiple products, as well as drug interactions;
2) requiring a 1-800 number on supplement labels for direct reporting to agency of adverse events experienced by consumers;
3) funding for inspections and good manufacturing practices development and oversight; and
4) authority to recall, seize, and levy penalties on products with synthetic adulterants, contaminants, mislabeling, and/or more than a trace amount of THC or other psycho-active cannabis derivatives.

**Recommended FDA Actions on Cannabis in Drugs:**

Unlike tobacco, some chemicals in the marijuana plant may offer some medical benefits. FDA's current approach to drug approval is generally sufficient to assure that the uses, risks, side effects, and efficacy of such compounds are adequately understood. As the National Academy of Sciences concluded in 1999: "the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology."[111]

It is inappropriate for states and localities to substitute their own comparatively uninformed medical judgement for the FDA drug approval process. FDA should balance its compassion for consumers with the under-developed state of the evidence and set out a vision to correct the imbalances and address the risks over time. The agency should develop a comprehensive multi-year program that will foster the evidence base, which could lead gradually to the replacement of medical marijuana programs in the states with a regulated program of oversight of approved drug uses by FDA. It is critical that cannabinoid products not be deregulated to the point that the incentives to develop the database for drug approval is diminished.

In sum, FDA should work to craft legal incentives to reward responsible research and winnow the medical uses to those supported by evidence and legitimized by a drug approval process. This should include the following steps:

1. FDA should work with other agencies and states and localities and researchers to develop survey and other data on the patient population served by medical marijuana programs, with an emphasis on understanding how vulnerable populations such as children, those with chronic pain, disease or other conditions, or the elderly, are using the drug. The agency should also study the products' side effects, dosage and other relevant information, as well as the adequacy of safety testing, including contamination. As it identifies safety gaps, it should work with states to close them.
2. As an interim measure, the agency should work with medical marijuana states and localities to ensure that the list of medical conditions being "treated" under those regimes is consistent with the state of the evidence, as evaluated by the NASEM or other relevant and credible evidence developed since issuance of that report.
3. Where side effects of uses are known, FDA should work with states to require adequate warnings and inform medical practitioners and patients of the risks and need for medical monitoring.
4. FDA should also, where warranted, issue warning letters to address claims on products being sold for disease and treatment purposes, prioritizing those for which the evidence is weakest or the risks most acute, as well as those for which existing medical treatments are more effective or safe.

Last, and most importantly, FDA should set a public deadline (*e.g.*, ten years out) by which all current claimed "medical" uses of cannabis listed by states that have legalized cannabis must be subject to a pending or approved drug application, after which time it will take appropriate actions to conduct enforcement. New drug applications would continue to be accepted after that time, to continue to allow approvals under federal law where evidence warrants it.

This would incentivize appropriate research into promising avenues for drug research, while allowing sufficient time to conduct such research. Critically, it would eventually bring cannabis regulation into conformity with federal drug law without undue disruption for individuals with medical concerns.

It would also clearly signal the value of investment into research by responsible companies by ensuring that the "medical" marketplace will eventually be supplanted by proven uses under federal law. It may signal to states that it is not worthwhile to begin with a "medical" approach, as that avenue has frequently proven to be clumsy, duplicative, and incomplete. Last, setting out a timetable and process for a full evaluation of drug uses would also ensure that, as FDA looks closely at edibles and other means of delivering cannabinoids to users, the medical marketplace does not grow in response.

**Recommended FDA Actions on Cannabis in Other Modalities:**

For cannabis that is smoked or vaped or consumes in any other way, FDA should seek additional appropriate authorities from Congress, and these authorities should include, at a minimum, harm

mitigation measures such as labeling, potency restrictions, warnings, packaging, sales restrictions, restrictions on flavorings, and other steps to ensure that recreational uses are as safe as possible and that users are made aware of the known risks. FDA should have ample authorities to regulate all additional means of using cannabis by consumers, to avoid the jurisdictional issues that occurred over tobacco regulation related to e-cigarettes. FDA and other involved federal agencies should also seek funding from Congress adequate for shared oversight, regulatory activity, and coordinated inspections.

**Recommended Congressional Actions on Cannabis Safety:**

In general, Congress should support a broad effort to bring public health tools to bear on cannabis consumption. In addition to funding the steps and new authorities outlined above, Congress should:

- Require federal agencies to develop a coordinated and robust communications and educational effort to inform the public more fully about what is known concerning the safety and risks of cannabis.
- Fund FDA and federal research agencies to conduct and develop appropriate research around the risks and potential benefits of cannabis use, as well as the best means of communicating these risks to consumers. Researchers should be allowed to access products from a wide range of sources including legally produced and tested products in states where sale is legal as well as other tested formulations. It must be made more feasible to scientifically evaluate the safety and effectiveness of cannabis products being sold today, and not solely products that currently bear little resemblance to the market, within the normal guidelines for development of new medicines. Federal research funding should be available.
- Support a consortium of federal and state agencies, including law enforcement, to develop and deepen best practices around driving under the influence prevention, including funding for enforcement and public education.

**Conclusion: A Role for the FDA in Cannabis Safety**

There is clear and demonstrated public interest and support for legalization of cannabis, yet both consumers and the states would benefit from additional core protections. The Food and Drug Administration is appropriately charged under our national scheme with a primary role in protecting consumers from the risks and hazards of foods, drugs, and dietary supplements.

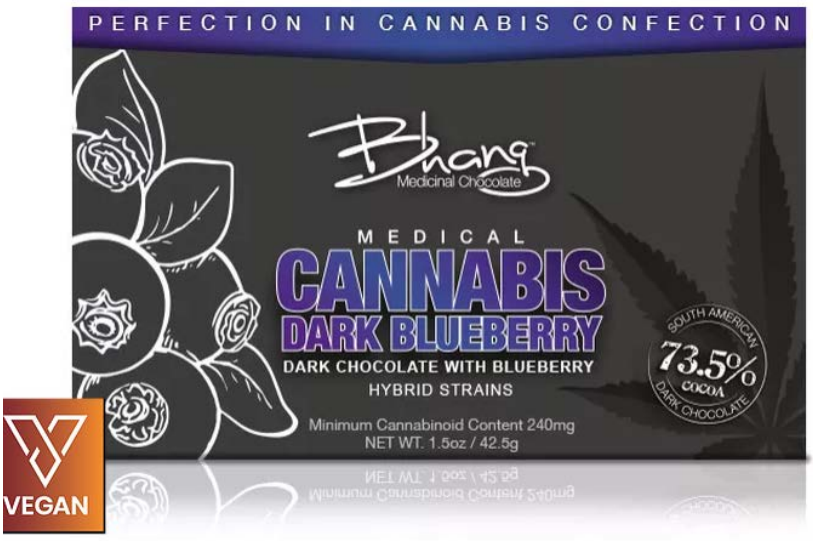
We urge the agency to adopt a sensible, public-health approach, using existing authorities wherever possible, and requesting additional authority where needed, to create productive alignment between state and federal law over time. FDA should also use its enforcement mechanisms as well as informational tools to minimize risks and public misunderstanding. Most importantly, the agency should specifically prioritize actions that reduce risks to children.

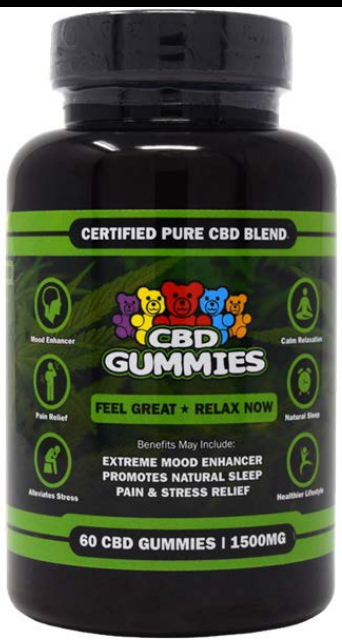
## Appendix A. Examples of products that appeal to children





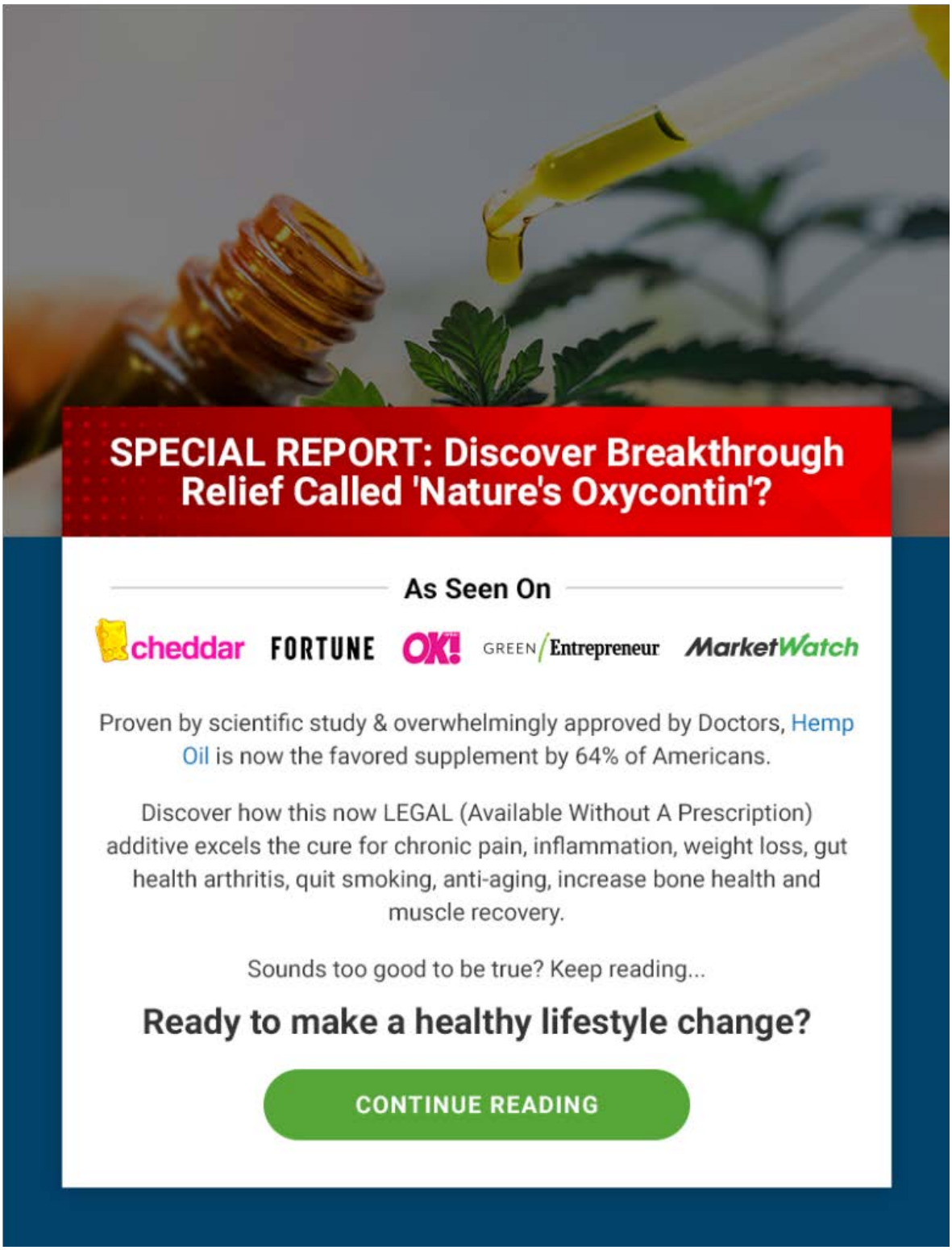
## Appendix B. Examples of high potency products

## Appendix C. Example of a product marketed for use by high-risk groups

**Appendix D: Example of a CBD Advertisement including disease and treatment claims**

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