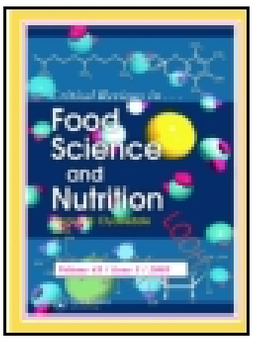

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REVIEW

Mitigating potential public health problems associated with edible cannabis products through adequate regulation: A landscape analysis

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ABSTRACT

An edible cannabis product (ECP) manufactured with food ingredients is subject to the same types of contamination as any conventional food product. Physical, microbial, and chemical hazards are a potential threat to anyone consuming cannabinoid-containing products by mouth. Preventing the unintentional ingestion of ECPs is also a concern for public health professionals. An analysis of the regulatory landscape in the United States (US) was conducted to identify best practices specific to ECPs and to pinpoint preventative safety measures that had not been extensively implemented. Widespread adoption of some of the more useful precedents set by US jurisdictions, as examined in this work, could be of great value in protecting public health.

KEYWORDS

Food; marijuana; cannabinoid; policy; tetrahydrocannabinol; cannabidiol

Introduction

Millions of Americans regularly consume cannabinoid-containing products that have not been approved by the Food and Drug Administration (FDA).[1] As of this writing, cannabis is classified as a Schedule 1 Drug in the US, meaning it has no currently accepted medical use, a high potential for abuse, and a lack of accepted safety even when used under medical supervision.[2] Despite that fact, at least 44 states, the District of Columbia (DC), and 3 US territories have passed legislation providing legal protection for qualified individuals who possess and use cannabinoid-containing products that have not been approved by the FDA to treat certain medical conditions.[3–89] Regardless of whether a jurisdiction regulates cannabis, cannabinoid-containing products are being advertised and consumed for their putative medical benefits. This is particularly evident with the epidemic of unregulated industrial hemp-derived cannabidiol (CBD) products currently seen across the US.

Conflict between state and federal law

Regulatory agencies face many difficulties when trying to regulate cannabis products. Adding food ingredients into this equation causes even more unique issues to arise. By federal standards, cannabis is currently considered an adulterant to food.[90] This has prevented many regulatory agencies from taking an active role in regulating ECPs. Notwithstanding, at the time of this writing at least 7 jurisdictions had legislation explicitly stating that the addition of cannabis or cannabis extracts to food shall not make it adulterated.[5–8,11,13,20,32,33,59–62,91] Additionally, at least 22 jurisdictions had incorporated their conventional food-safety regulations into their cannabis legislation by reference.[5–11,13–17,20,22,23,25,30–33,35–37,42–45,49,50,58–62,74,75,77–79,83–85,91,92] While more research is needed to determine how the compounds in cannabis affect and are affected by different food matrices, existing food-safety guidelines can help to ensure ECPs are safe regardless of whether, by definition, they are considered "adulterated food."

Public health implications

Food safety should be of particular concern with ECPs for many reasons. Inherently vulnerable people may be consuming cannabinoid-containing products for their potential medical benefits. The most commonly cited medical indications for cannabinoid use in the 48 jurisdictions that had applicable legislation identifying specific conditions (as of February 2019) are presented in Figure 1.

All jurisdictions that provided legal protection for qualified patients using non-FDA-approved cannabinoid-containing products allowed for minors to be patients.[3–23,25,27,30–67,70–85,87,88] Young children are considered a high-risk population from a food-safety perspective.[93]

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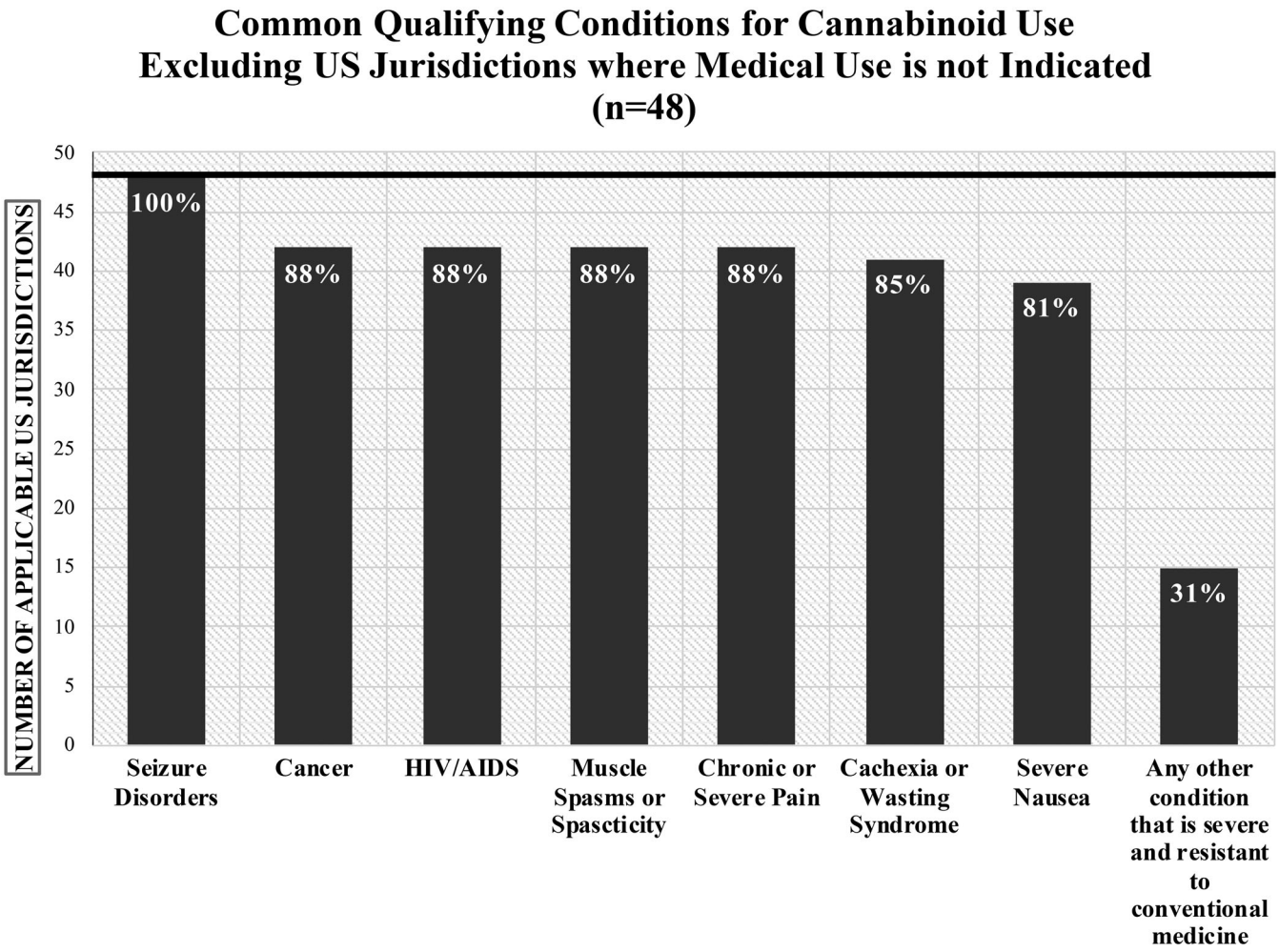

Figure 1. Common qualifying conditions for cannabinoid use excluding US jurisdictions where medical use is not indicated.
Description: Authors' analysis of legislation from 48 US jurisdictions that provide legal protection for the medical use of non-FDA-approved cannabinoid-containing products by qualified individuals.
References: 3–23,25,27,30–67,70–85,87,88.

All included jurisdictions listed seizure disorders as a qualifying condition. Eighty-eight percent of these jurisdictions listed cancer, HIV/AIDS, muscle spasticity, and severe or chronic pain as qualifying medical conditions.[3–23,25,27,30–40,42–45,47–54,56–67,73–81,83–85,87,88] Many patients with cancer or HIV are immunocompromised and may be especially vulnerable to pathogenic or opportunistic microorganisms.[93,94] In a clinical setting it is common practice to provide food-safety education to these patients.[94] Many jurisdictions indicated muscle spasticity or spasms when specifically associated with multiple sclerosis (MS), however some jurisdictions listed various spasm-causing disorders, and others simply listed "muscle spasms" in their regulations.[3–23,25,27,30–40,42–45,47–54,56–67,73–81,83–85,87,88] Many MS patients are treated with immunosuppressive medications to delay the progression of the disease,[94] which can cause this population to be more susceptible to infection caused by foodborne microorganisms. Although severe or chronic pain does not inherently cause a person to be immunocompromised, as of 2016 more than 27% of the chronic pain patient population was 65 years of age or older;[95] the elderly are also considered a high-risk population from a food-safety perspective.[93] Cachexia and wasting syndrome were indicated as qualifying medical conditions for cannabinoid use in 85% of this sample,[3–20,22,23,25,27,30–40,42–45,47–54,56–67,73–81,83–85,87,88] and severe nausea was indicated in 81%.[3–20,22,23,27,32–40,42–45,47–54,56–67,73–81,83–85,87,88] In a clinical setting all three of these conditions are often indicative of malnutrition, which can affect an individual's ability to adequately respond to challenges brought on by foodborne illnesses.[94]

Although not commonplace, 31% of the included jurisdictions had language that created a category to allow virtually any ailment to be a qualifying medical condition for cannabinoid use.[3–15,20,34–37,42,43,59,60,74–79,81,85] Inherently vulnerable populations are likely to be consuming cannabinoid-containing products, as evidenced by Figure 1, thus it is a matter of urgency that adequate manufacturing requirements be standardized and implemented across the US.

Many compounds found in the *Cannabis sativa* L. plant have potential side effects that can affect all consumers. Cannabinoid-induced hyperemesis can occur following the

consumption of a product unexpectedly high in delta-9 tetrahydrocannabinol (THC), but is also seen in chronic cannabis users after they consume what they consider a "normal" amount of cannabis.[96] There are several theories for why this reaction of cyclic vomiting occurs, some focus on the high concentration of cannabinoid 1 (CB1) receptors in the area postrema of the medulla oblongata, however more research is needed. Severe psychological distress can be caused by the unexpected psychoactive effects that may occur after someone unintentionally consumes a cannabis product or receives a higher dose of cannabinoids than they anticipated. Another concern is the fact that cannabis has been found to increase the intoxicating effects of many different drugs, including alcohol.[97–101] In some situations, such as cases of a chronic pain patient experiencing increased analgesic effects when combining cannabinoids with their normal dose of pain medication, this can be beneficial.[98,99] A more troubling example is someone who remains under the legal blood alcohol level to drive but also consumes cannabinoids on the same day; the individual may suddenly experience a much more profound level of intoxication from either substance.[100]

Human beings have hundreds of cytochrome p450 (CYP) enzymes, which are at the center of most drug metabolism.[102,103] They turn pro-drugs into active moieties, and they can inactivate other drugs. Phytochemicals in cannabis can and do affect the activity of many CYP enzymes.[97,101] THC, Cannabinol (CBN), and CBD have been found to inhibit enzymes in the CYP3A subfamily, specifically CYP3A4, which is the most abundantly expressed of the human CYP enzymes.[97,102,103] The CYP3A subfamily accounts for almost half of the CYP enzymes found in the liver and intestinal epithelium and are involved in the metabolism of more than 50% of drugs that undergo alteration by oxidation.[102,103] Plasma concentrations and the resulting therapeutic effects of commonly used medications like statins (e.g., atorvastatin and lovastatin), antibiotics (e.g., erythromycin), calcium-channel blockers (e.g., felodipine), and some immunosuppressive drugs (e.g., cyclosporine and tacrolimus) may be affected by inhibition of the CYP3A subfamily. Additionally, THC, CBN, and CBD have been found to inhibit CYP2D6 and enzymes in the CYP2C subfamily.[97,101] CYP2D6 is responsible for the metabolism of many different types of medications, including a variety of antiarrhythmic agents, opioids, antipsychotic and antidepressant agents including selective serotonin reuptake inhibitors.[102,103] CYP2C9 is responsible for metabolizing the anti-coagulant warfarin, which has a narrow therapeutic index and is widely used. Improper metabolism of warfarin due to inhibition of CYP2C9 could result in life-threatening bleeding complications.[101,102] While clinical research characterizing the extent of potential cannabinoid-drug interactions is still in its infancy, cannabinoid interactions with CYP enzymes found in the intestinal tract and the liver can have profound effects on the metabolism, bioavailability, detoxification, and ultimate efficacy of many drugs, dietary supplements, and food components.[97,101–103]

Alternatives to ECPs

Cannabis can be consumed in many different ways. Smoking and vaporizing are popular options, however both behaviors are public health problems and those delivery methods cannot be widely condoned – certainly not if there are alternative delivery methods. Medical evidence identifying the potential extent of the damage smoking or vaporizing cannabis can inflict is minimal.[104] Above all, given the potential respiratory issues associated with smoke inhalation,[104,105] medical cannabis patients who are minors should not need to smoke or vaporize their medicine due to an absence of safe ECPs. Topical products are fairly common, however, relative to ECPs they have a limited scope of applications. Suppositories are an option, but that route of administration would not provide the protective barriers associated with normal digestion following the consumption of a cannabis product by mouth; for example, stomach acid helps defend against microbial hazards.[94]

Some jurisdictions explicitly banned ECPs but still allowed certain orally-consumed cannabis products to be manufactured.[18,19,22,23,27,30,31,34,40,51,54,63,64,71–73,76,80] Generally, these were limited to tinctures, pills, and lozenges. It is important to consider that many of those products are made with food ingredients and still have the potential of containing foodborne hazards. Questions that arise include: What is the difference between a lozenge and a hard candy? What is the difference between a chewable tablet and a chewable candy? Ultimately, a system should be developed that prevents purveyors of cannabis goods from taking advantage of ambiguous language. Rather than limiting product forms, adequate packaging and labeling requirements should defend against unintentional consumption, as they do with any product that is considered potentially harmful.

Materials and methods

Between January and March of 2019 we conducted phone interviews with regulatory officials from 35 states and DC, and reviewed legislation from 56 US jurisdictions (50 states, DC, and 5 US territories).[3–89] At that time, 51 of those jurisdictions had enacted legislation providing legal protection for the possession of non-FDA-approved cannabinoid-containing products.[3–23,25,27–67,70–88] Thirteen of those jurisdictions only allowed low-THC products, and therefore were excluded.[3,4,21,27–29,41,46,55,70–72,76,81,82] Of the remaining 38 jurisdictions, 10 limited the ECPs they would allow to product forms like tinctures, pills, and lozenges.[18,19,22,23,30,31,34,40,51,54,63,64,74,75,80] Of the remaining 28, 6 jurisdictions had not developed ECP-specific regulatory procedures to the point where complete information could be obtained at the time of this analysis.[9,10,20,42,43,56,57,86,88] We excluded the remaining 2 US territories because adequate information could not be gathered. The 20 jurisdictions that composed our final sample were: Alaska, Arizona, California, Colorado, Connecticut, Illinois, Maine, Massachusetts, Michigan, Montana, Nevada, New Hampshire, New Mexico, Ohio, Oklahoma, Oregon, Rhode Island, Vermont, Washington, and DC. The rest of this analysis will focus on their regulatory landscape specific to ECPs.

Results

The purpose of the following analysis was to summarize our understanding of how ECPs are regulated at the state level throughout the US. We identify policies common among jurisdictions and highlight practices that appear to be most effective at mitigating the potential for public health problems such as foodborne illness and accidental consumption. By evaluating the ECP regulations that have already been implemented, a standardized system could be established to help ensure public safety.

Manufacturing requirements

A major focus of the FDA Food Safety Modernization Act was to prevent foodborne hazards through safe food-handling procedures.[106] Reviewing manufacturing plans helps ensure that standard operating procedures (SOPs) keep products safe and guarantee sanitation. Important components are a description of all ingredients and recipes, portraying the flow of food through the establishment, and identifying potential hazards. Half of the sample reported that their conventional food regulatory agency reviewed ECP manufacturing plans in conjunction with their cannabis regulatory agency prior to awarding a license.[5–8,16,17,25,35–37,59–62,74,75,77–79,83,84] Half of the sample required pre-approval of any ECPs made available to consumers.[3,4,14–17,35–39,47,48,58,61,62,77–79,83,84]

A license of some type was mandatory for cannabis businesses in all included jurisdictions,[5–8,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,74,75,77–79,83,84] but 60% of the sample required a special license, permit, or endorsement specifically for manufacturing ECPs.[5–8,11,13–15,32,33,35–37,47,48,59–62,74, 75,77–79,83,84] Only Oklahoma and Maine reported allowing the production of ECPs in commercial kitchens that also produce conventional foods. However, prohibiting simultaneous use of equipment and strict cleaning requirements appease concerns about cross contamination. Furthermore, there are restrictions on the types of establishments that can produce ECPs, such as forbidding minors from entering the premises, which in theory would prevent ECP production in most retail food establishments.

Inspections

Inspections play an extremely important role in ensuring the safety of both conventional food and ECPs. Fifty-five percent of our sample reported their conventional food regulatory agency was involved in the ECP manufacturer inspection process, either by performing inspections alongside the cannabis regulatory agency or independently.[5–8,16,17,25,32,33,49,50,59–62,74,75,77–79,83,84]

Food-safety training

Requiring that workers who handle ECPs receive formal food-safety training can help prevent occurrences of foodborne illness outbreaks. In total, 65% of the sample enforced a food-safety training requirement for ECP manufacturers.[5–8,11,13–17,25,32,33,35–39,47,48,52,53,58,83,84] Twenty-five percent required one certified food-safety manager to be on staff during all hours of operation,[16,17,25,32,33,47,48,83,84] and 40% required all applicable employees to have a food-handler license.[5–8,11,13–15,35–39,52,53,58]

Lab testing

Lab testing requirements are another important step in ensuring the safety and consistency of ECPs. Unfortunately, this area of cannabis regulation is in dire need of standardization. At least 70% of our sample required that ECPs be tested for cannabinoid content in their final form, however the specific requirements varied.[5,6,11,13–15,35–39,44,45,47,48,52,53,58–62,65–67,77–79,83,84] Sixty percent required microbial testing of some sort, but no two jurisdictions tested for the same panel of microorganisms while using the same pass/fail criteria.[5,6,11,13–15,35–39,44,45,47,48,52,53,58–60,65–67,83,84] Half of our sample required that ECPs be tested for homogeneity, but different protocols were being used across the country.[5,6,11,13–15,35–39,47,48,61,62,65–67,77–79,83,84] The United States Pharmacopeia (USP) has recently published recommended standards that, among other things, identify appropriate lab testing principles and procedures to determine the content of important constituents in cannabis that is intended for medical use.[107] While these standards discuss therapeutic compounds, including cannabinoids and terpenes, they also present limits for contaminants commonly found in cannabis, including microorganisms, mycotoxins, foreign matter, pesticide residues, and elemental impurities. These USP recommended standards are an important step toward alignment in cannabis testing requirements throughout the US.

ECP requirements and restrictions

Seventy percent of our sample required that the ECP itself not be attractive to children.[5,6,11,13–17,32,33,35–39,47–50,58–62,77–79,83,84] In most cases this prohibited ECPs bearing a likeness to, or having an image of, a human, animal, or food, including cartoon renderings. Forty-five percent of the sample forbade the sale of commercially available food products sprayed with a cannabis extract, likely to prevent consumers from unintentionally ingesting an ECP they thought was a conventional food product.[11,13–15,25,32,33,47,48,59,60,65–67,77–79,83,84] Forty percent of these jurisdictions prohibited ECPs that resemble specific types of candy, like lollipops or cotton candy.[5,6,16,17,35–39,47,48,58,77–79,83,84] In 30% of the sample potentially-hazardous ECPs were banned.[16,17,25,38,39,44,45,58,77–79] This included ECPs that require unique packaging processes (e.g., canning) or temperature control for safety (TCS). Because TCS-foods need to be stored in a refrigerator or freezer, consumers will likely keep potentially-hazardous ECPs next to conventional

foods, which increases the potential for microbial contamination and accidental consumption of an ECP.

We asked jurisdictions that did not ban potentially-hazardous ECPs to indicate what types of high-risk cannabis products they saw, but most of them reported that potentially-hazardous ECPs are not very common. Some of these jurisdictions required that manufacturers of potentially-hazardous ECPs submit a hazard analysis and critical control points (HACCP) plan (or a similar written plan), which may inherently deter manufacturers from producing these high-risk ECPs. Many of these jurisdictions reported that cannabis consumers seem to prefer the ease of handling shelf-stable ECPs, like cannabis-infused chocolates or lozenges, rather than the novelty of higher-risk ECPs, like cannabis-infused cheese or tomato sauce, thus apparently limiting the demand for potentially-hazardous ECPs.

ECP packaging requirements

Packaging requirements for ECPs are fundamental to preventing unintentional consumption. Ninety-five percent of this sample required ECPs to be housed in child-resistant packaging,[5,6,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,74,75,77–79,83,84] 65% required opaque packaging,[5,6,11,13–17,25,32,33,35–39,47–50,52,53,58,65–67] and 55% required tamper-evident packaging.[11,13,16,17,25,32,33,35–39,49,50,58,65–67,77–79,83,84] The combination of these three requirements would result in a package that: (a) cannot be seen into, (b) children will have difficulty opening, and (c) would indicate if someone had opened the ECP. Fifty-five percent of these jurisdictions required ECP packaging to help identify servings, which sometimes included wrapping individual servings or providing a measuring device.[5,6,11,13–15,32,33,35–37,47,48,58,61,62,65–67,77–79,83,84] Additionally, 90% of this sample required that ECP packaging be composed of materials approved for use with conventional food products.[5,6,11,13–17,25,32,33,35–39,44,45,47–50,58–62,65–67,74,75,77–79,83,84]

ECP labeling requirements

Labels are the last line of defense between consumers and a product; they should serve to properly inform people. All included jurisdictions required an ECP's label to identify the product's manufacturer.[5–8,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,74,75,77–79,83,84] Ninety-five percent required the cannabinoid content to be listed.[5,6,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,74,75,77–79,83,84] The specific cannabinoids required to be reported on the label varied, and as previously stated, only 70% of the sample had mandated label claims be supported by lab testing.[5,6,11,13–15,35–39,44,45,47,48,52,53,58–62,65–67,77–79,83,84] Sixty-five percent required the number of servings, usually based on THC content, be listed.[5,6,11,13–15,32,33,35–37,47–50,52,53,58–62,65–67,77–79] Ninety percent of the sample required some type of lot/batch identification number to be on ECP labels,[5–8,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,77–79] 85% required the net weight of the product be indicated,[5–8,11,13–15,32,33,35–39,44,45,47–50,58–62,65–67,74,75,77–79,83,84] 80% required that all ingredients be listed,[11,13–15,25,32,33,35–39,44,45,47–50,58–62,65–67,74,75,77–79,83,84] and 5% required any common food allergens be identified.[11,13–15,25,32,33,35–39,44,45,47–50,58–62,65–67,77–79,83,84] Also, 80% required the manufacturing date be listed,[5–8,11,13–17,25,32,33,44,45,47–50,52,53,58,61,62,65–67,74,75,83,84] 70% required an expiration date be specified,[5,6,11,13–17,25,32,33,35–39,47–50,52,53,58,65–67,77–79] and 45% required that storage instructions for the ECP be indicated.[11,13,16,17,35–37,44,45,47–50,52,53,65–67,74,75]

The following labeling requirements were not as widely implemented, but very important measures to consider when trying to avoid potential adverse reactions associated with ECPs.

Cannabis concentrate identification

Forty-five percent of our sample required that ECPs identify if they use a cannabis concentrate of any sort.[14,15,32,33,35–37,47–50,58,61,62,65–67,77–79] This is important because different extraction methods yield products with quite different phytochemical compositions. Research has indicated the potential for varying psychotropic effects while increasing the therapeutic index of cannabinoids due to a concept known as the entourage effect, which suggests that different phytochemicals found in cannabis have the ability to modulate one another.[108] This is particularly evident when considering that CBD can modify the effects of THC by acting as a negative allosteric modulator of the CB1 receptor, or by inhibiting the CYP2C9 enzyme, which converts THC into its more "potent" metabolite 11-hydroxy THC.[101,109] As a result, some people may have fewer side effects when consuming ECPs made with a specific type of cannabis extract.

Cultivar of cannabis

Twenty-five percent of our sample required that the variety of cannabis used in an ECP be identified.[7,8,38,39,49,50,58,74,75] Since many consumers purchase cannabis-containing products for a desired effect, advance knowledge of the cultivar(s) of cannabis used will help them know what to expect. Although there are also purported to be substantial phenotypical variations between the same varieties of cannabis grown in different places, generally due to environmental conditions, it may be instructive to look at them similarly to the way we look at wine grapes. Pinot noir grapes grown in France will produce a wine with different characteristics than pinot noir grown in California, however they both have common traits sommeliers use to identify them.

Poison Control Center contact information

Only one quarter of our sample required that the National Poison Control Center phone number be listed on ECP labels.[35–39,59,60,77–79,83,84] Establishing one main reporting system is a critical step toward the nationwide monitoring of adverse events related to cannabinoid-containing products, and fundamental to gaining important information about health risks, drug-cannabinoid interactions, and populations that should not consume cannabis.

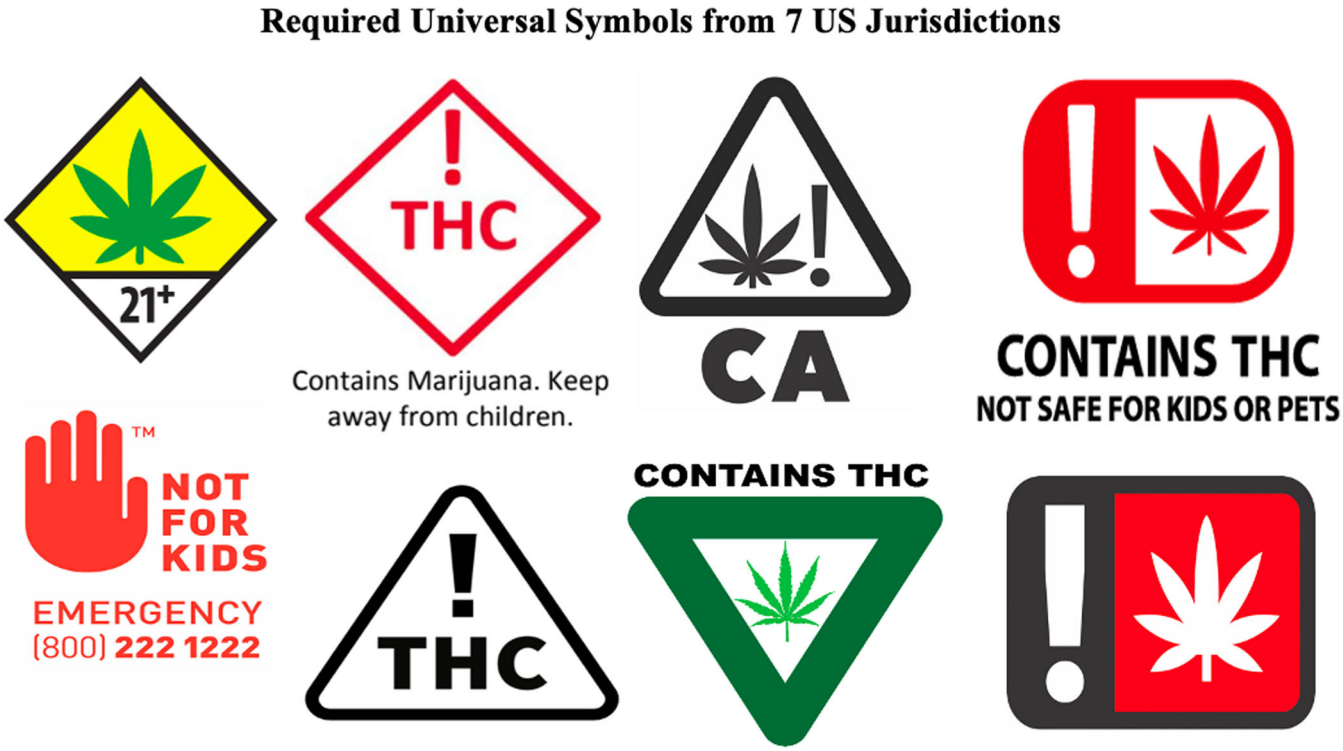

Figure 2. Required universal symbols from 7 US jurisdictions.
Description: Images of state-mandated cannabis identification symbols from 7 US jurisdictions.
References:
State of California. *Universal Cannabis Symbol*, Image on Internet. Accessed February 28, 2019. https://www.cdph.ca.gov/mcsb. © California Department of Public Health. All Rights Reserved. Reproduced with permission received on July 13, 2020.
State of Colorado. *Medical and Recreational Marijuana Single Universal Symbol Examples*, Image on Internet. Accessed February 28, 2019, https://www.colorado.gov/pacific/sites/default/files/Universal%20Symbol%20Image%20March%202018.PNG. © Colorado Department of Revenue. All Rights Reserved. Reproduced with permission received on July 16, 2020.
State of Michigan. 2019. *Universal Cannabis Symbol*, Image on Internet. Accessed February 28, 2019. https://www.michigan.gov/images/lara/Conatins_THC_613985_7.jpg. No Rights Reserved. This image is in the Public Domain.
State of Nevada. *Universal Marijuana Symbol*, Image on Internet. Accessed February 28, 2019. http://marijuana.nv.gov/uploadedFiles/marijuananvgov/Content/Safety_Information/SymbolFinal.pdf. © Nevada Department of Taxation. All Rights Reserved. Reproduced with permission received on July 10, 2020.
State of Oklahoma. *Universal Cannabis Symbol*, Image on Internet. Accessed February 28, 2019. http://omma.ok.gov/thc-universal-symbol. © OMMA. All Rights Reserved. Reproduced with permission received on July 16, 2020.
State of Oregon. *Cannabis Universal Symbol*, Image on Internet. Accessed February 28, 2019. https://www.oregon.gov/oha/ph/preventionwellness/marijuana/pages/symbol.aspx. © Oregon Health Authority. All Rights Reserved. Reproduced with permission received on July 13, 2020.
State of Washington. *Universal Symbol*, Image on Internet. Accessed February 28, 2019. https://lcb.wa.gov/laws/labeling-resources. © Washington State Liquor and Cannabis Board. All Rights Reserved. Reproduced with permission received on July 10, 2020.
Washington Poison Center. *Not for Kids Symbol*, Image on Internet. Accessed February 28, 2019. https://www.wapc.org/programs/services/not-for-kids/. © Washington Poison Center. All Rights Reserved. Reproduced with permission received on July 13, 2020.

Nutrition facts

Thirty-five percent of our sample required ECP labels include some nutrition information.[11,13–15,32,33,35–37,52,53,59–62] For patients with medical conditions that require dietary interventions, knowing the nutritional value of any product they consume is crucial. However, label space is valuable real estate. This may be a requirement that should be evaluated and prioritized on an ECP-by-ECP basis.

Universal cannabis symbol

The presence of a universal cannabis symbol on any cannabinoid-containing product would ideally inform consumers and prevent unintentional consumption. Half of our sample required that ECP labels contain a universal symbol;[11,13–15,32,33,35–39,47,48,58–62,77–79] Figure 2 portrays the universal symbols from seven of those jurisdictions.

While there are similarities, it is clear no single universal cannabis symbol exists. This may demonstrate a lack of standardization between jurisdictions, but it also serves a purpose. Since cannabis is currently federally illegal, cannabis products are not allowed to cross state lines. Thus, the existence of different universal symbols helps to identify where a cannabis product originated.

Warning statements

Misinformation about cannabinoids is rampant, and warning statements can help inform consumers about inherent risks associated with ECPs. Table 1 portrays the most common types of warning statements required on ECP labels; the specific language used was not standardized. Jurisdictions in our sample that included these statements

Table 1. Common warning statements required on ECP labels.

15/20 Jurisdictions (75%)	Keep away from children.
14/20 Jurisdictions (70%)	Diversion statement: it is illegal to transfer the product to anyone other than a qualified patient, across state lines, or, if applicable, to anyone under the age of 21.
12/20 Jurisdictions (60%)	Warning about the delayed onset of effects when consuming an edible cannabis product.
11/20 Jurisdictions (55%)	Do not operate a vehicle or heavy machinery under the influence of cannabis.
7/20 Jurisdictions (35%)	There may be unknown health risks associated with cannabis use.
6/20 Jurisdictions (30%)	Cannabis should not be used by females who are pregnant or nursing.
6/20 Jurisdictions (30%)	Cannabis has intoxicating effects and may be habit-forming.

Description: General language included in the most common warning statements required on labeling of ECPs.
References: 5–8,11,13–17,25,32,33,35–39,44,45,47–50,52,53,58–62,65–67,74,75,77–79,83,84.

on a cannabis-safety information sheet provided with exit packaging were not included in these data.

Restrictions to ECP packaging and labeling

Restrictions to packaging and labeling play a major role in preventing confusion of an ECP with a conventional food product. Eighty-five percent of the sample required that ECP packaging not be attractive to children.[5,6,11,13–17,25,32,33,35–37,44,45,47–50,58–62,65–67,77–79,83,84] This generally prohibited pictures of animals, humans, cartoons, foods, and any pattern or color scheme that could be appealing to children. Eighty percent of our sample forbade ECP labels from containing misleading statements like health claims,[5,6,11,13–17,32,33,35–37,44,45,47–50,58–62,65–67,77–79,83,84] 65% prohibited ECPs from being marketed as "candy,"[5,6,11,13–17,25,32,33,35–39,47,48,58,65–67,77–79,83,84] and 50% banned ECP packaging or labeling that is similar to any commercially available food product.[5,6,11,13–17,32,33,35–39,49,50,65–67,83,84]

Discussion

While many jurisdictions took a more prudent approach to regulating ECPs than most conventional foods, cannabis product manufacturers should be held to a higher standard for multiple reasons. We have emphasized the fact that consumers of cannabis products are more likely to be inherently vulnerable than the general population (Figure 1). Additionally, ensuring the homogeneity of ECPs is critical since many ECP labels claim to have a specific cannabinoid titer. Furthermore, cooking processes can affect the distribution of compounds within a batch of ECPs. Precautionary measures such as evaluating all SOPs for safety and testing ECPs for homogeneity are not unreasonable requirements. Pre-approval of ECPs prevents products from entering the market that may be especially attractive to children or easily confused for a conventional food product by the general population. The proliferation of unregulated hemp-derived CBD products being sold throughout this country justifies taking a deeper look at the regulatory landscape specific to cannabis products in an effort to establish nationwide standards that apply to all cannabinoid-containing products.

There are many other dynamics involved with regulating ECPs that are not discussed herein. Limits on the cannabinoid content of an ECP are important, however they may cause a burden to people who have higher tolerances or limited mobility. Also, due to the lack of standardization between ECP sample collection, sample preparation, and testing methods used by cannabis testing laboratories, there is a high potential that measurement error will skew test results.

Little is known about how the other phytochemicals in cannabis affect, or are affected by, different food matrices. A legal cannabis testing laboratory has characterized how different chocolate matrices, specifically milk chocolate, dark chocolate, and cocoa powder, can interfere with routine cannabinoid testing.[110] It is apparent that further research is needed to fully understand how the different food ingredients used to make ECPs affect the accuracy of compliance testing. Ultimately, an expected variability threshold for cannabinoid content should be established and indicated on ECP labels. Additionally, the content of therapeutic compounds in an ECP may change over time, therefore stability studies are critical.

It is logical to assume that if cannabis plant material and/or extract is initially tested, and any food ingredients come from a source that adheres to standards for products intended for human consumption, then ECPs made from them would be safe given proper food-handling and sanitation procedures are followed. However that might not be the case; reports of foodborne hazards associated with products made by major food manufacturers occur regularly in the US.[93]

Rigorously testing ECPs in their final form could help proactively identify and recall contaminated batches of food ingredients much faster than normal epidemiological investigations, which would help prevent foodborne hazards from affecting the general public. Unfortunately, there is no way to test for every potentially pathogenic microorganism, and variability will likely occur within and between production lots. Regulatory efforts should focus on preventative measures that help ensure the safety of ECPs.

Conclusion

Despite a lack of federal oversight, many US jurisdictions have developed robust regulatory systems for ECPs. It is remarkable that so many government agencies, laboratories, and cannabis product manufacturers have come together with a seemingly common goal: harm reduction. While regulatory efforts have not always initially focused on preventing foodborne hazards, in most applicable jurisdictions the need for regulations that support safety and sanitation

was quickly recognized. At this interface between public health and food safety, all US jurisdictions should consider precedents set by other states when developing their own systems to regulate cannabis products.

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References

1. Substance Abuse and Mental Health Services Administration. 2019. National Survey on Drug Use and Health, 2017 and 2018: Table 1.1A–Types of illicit drug use in lifetime, past year, and past month among persons aged 12 or older. Report No. 190725, Center for Behavioral Health Statistics and Quality, Rockville, MD. Accessed September 28, 2019. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect1pe2018.htm.
2. *Schedules of Controlled Substances* [US] 21 USCA §812.
3. *Leni's Law* [AL] AL ST §13A-12-214.3.
4. *Carly's Law* [AL] AL ST §13A-12-214.2.
5. *The Regulation of Marijuana* [AK] AK ST T. 17, Ch. 38.
6. *Regulation of the Marijuana Industry* [AK] 3 AK ADC 306.
7. *Department of Health Services Medical Marijuana Program* [AZ] AZ ADC T. 9, Ch. 17.
8. *Arizona Medical Marijuana Act* [AZ] AZ ST T. 36, Ch. 28.1.
9. *Rules and Regulations Governing the Oversight of Medical Marijuana Cultivation Facilities and Dispensaries by the Alcoholic Beverage Control Division* [AR] AR ADC 006.02.7.
10. *Rules and Regulations Governing Medical Marijuana Registration, Labeling, and Testing in Arkansas* [AR] AR ADC 007.16.4.
11. *Manufactured Cannabis Safety* [CA] CA ADC T. 17, D. 1, Ch. 13.
12. *The Compassionate Use Act of 1996* [CA] CA HLTH & S §11362.5.
13. *Cannabis [CA]* CA BUS & PROF D. 10.
14. *Medical Marijuana Rules* [CO] 1 CO ADC 212–1.
15. *Retail Marijuana Rules* [CO] 1 CO ADC 212–2.
16. *Palliative Use of Marijuana* [CT] CT ADC §§21a-408-1 to 21a-408-72.
17. *Palliative Use of Marijuana* [CT] CT ST T. 21a, Ch. 420f.
18. *Rules and Regulations Governing the Delaware Medical Use of Marijuana* [DE] 16 DE ADC 4470.
19. *The Delaware Medical Marijuana Act* [DE] DE ST T. 16, Pt. IV, Ch. 49a.
20. *Medical Use of Marijuana* [FL] FL ST §381.986.
21. *Regulation of Low Thc Oil* [GA] GA ST T. 16, Ch. 12, Art. 8.
22. *Medical Use of Cannabis* [HI] HI ST D. 1, T. 19, Ch. 329, Pt. IX.
23. *Medical Cannabis Dispensary System* [HI] HI ST D. 1, T. 19, Ch. 329D.
24. *Prohibited acts A—Penalties* [ID] ID ST §37-2732.
25. *Compassionate Use of Medical Cannabis Pilot Program* [IL] 77 IL ADC Ch. I(4), Subch. U, Pt. 946.
26. *Crimes and Offenses—Drugs and Medicine—Marijuana* [IN] 2018 Ind. Legis. Serv. P.L. 153-2018 (S.E.A. 52).
27. *Medical Cannabidiol Program* [IA] IA ADC 641–154.
28. *Industrial Hemp* [KS] KS ADC 4–34.
29. *Industrial Hemp* [KY] 302 KY ADC 50.
30. *Medical Marijuana* [LA] 7 LA ADC Pt. XLIX.
31. *Therapeutic Use of Marijuana* [LA] LA R.S. T. 40, Ch. 4, Pt. X-E.
32. *Office of Marijuana Policy* [ME] ME ADC 18–691.
33. *Adult Use Marijuana* [ME] ME ST T. 28-B.
34. *Natalie M. LaPrade Medical Cannabis Commission* [MD] MD ADC T. 10, Subt. 62.
35. *Adult Use of Marijuana* [MA] MA ADC T. 935, Ch. 500.00.
36. *Medical Use of Marijuana* [MA] MA ADC T. 935, Ch. 501.00.
37. *Colocated Adult-Use and Medical-Use Marijuana Operations* [MA] MA ADC T. 935, Ch. 502.00.
38. *Bureau of Medical Marihuana Regulation* [MI] MI ADC R 333.
39. *Health* [MI] MI ST, Ch. 333.
40. *Medical Cannabis* [MN] MN ADC, Ch. 4770.
41. *Harper Grace's Law* [MS] MS ST §41-29-136.
42. *Right to access medical marijuana* [MO] MO CONST Art. 14, §1.
43. *Medical Marijuana* [MO] 19 MO ADC D. 30, Ch. 95.
44. *Montana Marijuana Act* [MT] MT ST T. 50, Ch. 46, Pt. 3.
45. *Marijuana Registry* [MT] MT ADC 37.107.
46. *Medical Care and Treatment—Controlled Substances—Marijuana* [NE] 2015 Nebraska Laws L.B. 390.
47. *Medical Use of Marijuana* [NV] NV ADC 453A.
48. *Regulation and Taxation of Marijuana* [NV] NV ADC 453D.
49. *Therapeutic Cannabis Program* [NH] NH ADC Ch. HE-C 400.
50. *Use of Cannabis for Therapeutic Purposes* [NH] NH ST T. X, Ch. 126-X.
51. *Medicinal Marijuana* [NJ] NJ ADC T. 8, Ch. 64.
52. *Medical Use of Cannabis* [NM] NM ADC 7.34.
53. *Lynn and Erin Compassionate Use Act* [NM] NM ST Ch. 26, Art. 2B.
54. *Medical Use of Marihuana* [NY] NY ADC T. 10, Ch. XIII, Pt. 1004.
55. *Exemption for use or possession of hemp extract* [NC] NC ST §90-94.1.
56. *Medical Marijuana* [ND] ND ST Ch. 19-24.1.
57. *Medical Marijuana* [ND] ND ADC Ch. 33-44-01.
58. *Medical Marijuana Control Program* [OH] OH ADC 3796.
59. *Oklahoma Medical Marijuana and Patient Protection Act* [OK] OK ST T. 63 §§427.1-427.23.
60. *Medical Marijuana Control Program* [OK] OK ADC T. 310, Ch. 681.
61. *Recreational Marijuana* [OR] OR ADC 845–025.
62. *Cannabis Regulation* [OR] OR ST T. 37, Ch. 475B.
63. *Medical Marijuana* [PA] 28 PA ADC Pt. IX.
64. *The Medical Marijuana Act* [PA] PA ST T. 35 P.S., Ch. 64.
65. *Medical Marijuana Program* [RI] RI ADC T. 216, Ch. 20, Subch. 10, Pt. 3.
66. *Licensing Analytical Laboratories for Sampling and Testing Medical Marijuana* [RI] RI ADC T. 216, Ch. 60, Subch. 05, Pt. 6.
67. *The Edward O. Hawkins and Thomas C. Slater Medical Marijuana Act* [RI] RI ST T. 21, Ch. 28.6.
68. *Julian's Law* [SC] SC ST T. 44, Ch. 53, Art. 18.
69. *Controlled Substances and Marijuana* [SD] SD ST T. 22, Ch. 22–42.
70. *Marijuana* [TN] TN ST §39-17-402(16).
71. *Texas Compassionate-Use Act* [TX] TX HEALTH & S T. 6, Subt. C, Ch. 487.

72. *Compassionate-Use/Low-Thc Program* [TX] 37 TX ADC Pt. 1, Ch. 12.
73. *Utah Medical Cannabis Act* [UT] UT ST T. 26, Ch. 61A.
74. *Therapeutic Use of Cannabis* [VT] VT ST T. 18, Pt. 5, Ch. 86.
75. *Rules Regulating Cannabis for Symptom Relief* [VT] VT ADC T. 17, Subt. 2, R. 3.
76. *Regulations Governing Pharmaceutical Processors* [VA] VA ADC T. 18, Agcy. 110, Ch. 60.
77. *Marijuana Licenses, Application Process, Requirements, and Reporting* [WA] WA ADC Ch. 314–55.
78. *Health, Department of* [WA] WA ADC T. 246.
79. *Food, Drugs, Cosmetics, and Poisons* [WA] WA ST T. 69.
80. *Medical Cannabis Act* [WV] WV ST Ch. 16A.
81. *Prescriptions* [WI] WI ST 961.38.
82. *Health and Sanitation—Medical Care and Treatment—Plants and Plant Products* [WY] 2015 Wyoming Laws Ch. 102 (H.B. 32).
83. *Medical Marijuana* [DC] DC ADC T. 22, Subt. C.
84. *Use of Marijuana for Medical Treatment* [DC] DC CODE Div. 1, T. 7, Subt. G-II.
85. *The Joaquin (KC) Concepcion II Compassionate Cannabis Use Act of 2013* [GU] GU ST Div. 1, Ch. 12, Art. 25.
86. *Taulamwaar Sensible CNMI Cannabis Act of 2018* [CNMI] 4 CMC §§53001–53076.
87. *Medical Cannabis Act* [PR] 24 PR ST T. 24, P.V, Ch. 112.
88. *MCPCA* [VI] VI ST T. 19, P. III, Ch. 34.
89. *Medicine and Drugs* [AS] ASCA T. 13, Ch. 10.
90. *The Federal Food, Drug, and Cosmetic Act* [US] 21 USCA Ch. 9.
91. Arizona Department of Health Services. The Definition of "Food". Last Modified April 27, 2018. Accessed February 20, 2019. https://www.azdhs.gov/documents/licensing/medical-marijuana/dispensaries/food.pdf.
92. *State of Maine Food Code* [ME] ME ADC 01-001 Ch. 331, §1-201.10(B)(47).
93. Food and Drug Administration. Food Safety: Importance for At-Risk Groups. Last Modified February 28, 2019. Accessed September 28, 2019. https://www.fda.gov/food/people-risk-food-borne-illness/food-safety-importance-risk-groups
94. Nelms, M., K. P. Sucher, and K. Lacey. 2014. *Nutrition Therapy and Pathophysiology*. 3rd ed. Boston, MA: Cengage Learning.
95. Dahlhamer, J., J. Lucas, C. Zelaya, R. Nahin, S. Mackey, L. DeBar, R. Kerns, M. V. Korff, L. Porter, and C. Helmick. 2018. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. *MMWR Morbidity and Mortality Weekly Report* 67 (36):1001–6. doi: 10.15585/mmwr.mm6736a2.
96. Sorensen, C. J., K. DeSanto, L. Borgelt, K. T. Phillips, and A. A. Monte. 2017. Cannabinoid hyperemesis syndrome: Diagnosis, pathophysiology, and treatment – A systematic review. *Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology* 13 (1):71–87. doi: 10.1007/s13181-016-0595-z.
97. Alsherbiny, M., and C. Li. 2018. Medicinal cannabis—Potential drug interactions. *Medicines* 6 (1):3. doi: 10.3390/medicines6010003.
98. Abrams, D. I., P. Couey, S. B. Shade, M. E. Kelly, and N. L. Benowitz. 2011. Cannabinoid-opioid interaction in chronic pain. *Clinical Pharmacology and Therapeutics* 90 (6):844–51. doi: 10.1038/clpt.2011.188.
99. Cichewicz, D. L. 2004. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sciences* 74 (11):1317–24. doi: 10.1016/j.lfs.2003.09.038.
100. Hartman, R. L., T. L. Brown, G. Milavetz, A. Spurgin, D. A. Gorelick, G. Gaffney, and M. A. Huestis. 2015. Controlled cannabis vaporizer administration: Blood and plasma cannabinoids with and without alcohol. *Clinical Chemistry* 61 (6):850–69. doi: 10.1373/clinchem.2015.238287.
101. Yamaori, S., K. Koeda, M. Kushihara, Y. Hada, I. Yamamoto, and K. Watanabe. 2012. Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metabolism and Pharmacokinetics* 27 (3):294–300. doi: 10.2133/dmpk.dmpk-11-rg-107.
102. Wilkinson, G. R. 2005. Drug metabolism and variability among patients in drug response. *The New England Journal of Medicine* 352 (21):2211–21. doi: 10.1056/NEJMra032424.
103. Slaughter, R. L., and D. J. Edwards. 1995. Recent advances: The cytochrome P450 enzymes. *The Annals of Pharmacotherapy* 29 (6):619–24. doi: 10.1177/106002809502900612.
104. Yayan, J., and K. Rasche. 2016. Damaging effects of cannabis use on the lungs. *Advances in Experimental Medicine and Biology* 952:31–4. doi: 10.1007/5584_2016_71.
105. Maertens, R. M., P. A. White, A. Williams, and C. L. Yauk. 2013. A global toxicogenomic analysis investigating the mechanistic differences between tobacco and marijuana smoke condensates in vitro. *Toxicology* 308:60–73. doi: 10.1016/j.tox.2013.03.008.
106. FDA Food Safety Modernization Act. [US] 124 Stat 3885.
107. Sarma, N. D., A. Waye, M. A. ElSohly, P. Brown, S. Elzinga, H. Johnson, R. J. Marles, J. E. Melanson, E. Russo, L. Deyton, et al. 2020. Cannabis inflorescence for medical purposes: USP considerations for quality attributes. *Journal of Natural Products* 83 (4):1334–51. doi: 10.1021/acs.jnatprod.9b01200.
108. Russo, E. B. 2011. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects: Phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology* 163 (7):1344–64. doi: 10.1111/j.1476-5381.2011.01238.x.
109. Nadulski, T., F. Pragst, G. Weinberg, P. Roser, M. Schnelle, E.-M. Fronk, and A. M. Stadelmann. 2005. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Therapeutic Drug Monitoring* 27 (6):799–810. doi: 10.1097/01.ftd.0000177223.19294.5c.
110. Dawson, D., and R. Martin. 2020. Investigation of chocolate matrix interference on cannabinoid analytes. *Journal of Agricultural and Food Chemistry* 68 (20):5699–706. doi: 10.1021/acs.jafc.0c01161.