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Regulating Cannabis Manufacturing: Applying Public Health Best Practices from Tobacco Control

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ABSTRACT

State legalization and regulation of cannabis, despite continued federal illegality, is a massive shift in regulatory approach. Manufactured cannabis, including concentrates, extracts, edibles, tinctures, topicals and other products, has received less attention than more commonly used dried flower, but represents emerging regulatory challenges due to additives, potency, consumption methods, and abuse and misuse potential. In November 2017, the California Department of Public Health (CDPH) released initial cannabis manufacturing regulations as part of a new state regulatory structure. As the largest U.S. medical cannabis market (and largest legal adult use market in the world beginning in 2018), California's regulatory approach will potentially influence national and global policy. Comparing CDPH's initial regulations to tobacco control best practices reveals that, while the regulations recognize the need to protect public health, prioritizing public health over business interests requires stronger approaches to labeling, packaging, and product formulations. Based on tobacco best practices, we recommend that cannabis regulations incorporate large and proportionately sized informational labels, a prominent universal cannabis symbol, rotating and pictorial health warnings, mandatory plain packaging, a comprehensive ban on characterizing flavors and addictive additives, and strict limits on the potency of inhalable products and those easily confused with non-cannabis products.

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Introduction

California is the largest U.S. medical cannabis market and, in 2018, will be the largest legal recreational ("adult use") market in the world, with potential to influence national and global policy. Medical cannabis legalization in California in 1996 (Ballotpedia.org 2017b) exempted qualified patients from state criminal penalties for possessing or growing cannabis, but did not establish state regulations for producers or dispensaries. The system relied on a patchwork of local rules with limited 2003 state legislation (California Department of Public Health 2017a; S.B. 420). Following passage of comprehensive medical cannabis legislation in 2015–16 (S.B. 643), three state agencies—the California Department of Public Health (CDPH), California Department of Food and Agriculture (CDFA), and newly created Bureau of Cannabis Control (BCC)—released draft medical cannabis regulations in April 2017 (California Bureau of Marijuana Control 2017; California Department of Food and Agriculture 2017a; California Department of Public Health 2017b). These agencies will also regulate adult use cannabis, legalized by 2016 ballot initiative (Ballotpedia.org 2017a). In June 2017, the legislature merged the medical and adult use regulatory systems under the Medicinal and Adult-Use Cannabis Regulation and Safety Act (S.B. 94), leading agencies to withdraw proposed medical regulations in favor of unified versions. New joint medical and adult use regulations were issued on an emergency basis in November 2017 (Bureau of Cannabis Control 2017; California Department of Food and Agriculture 2017b; California Department of Public Health 2017c) to meet statutory obligations to begin licensure in January 2018 and will become effective before (rather than following) a standard public comment process.

Manufactured cannabis product regulation has received limited scholarly attention (Budney, Sargent, and Lee 2015; Carlini, Garrett, and Harwick 2017; Friese et al. 2016; Gourdet et al. 2017; MacCoun

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and Mello 2015; National Academies 2017; Subritzky, Lenton, and Pettigrew 2016). Manufactured cannabis is plant material processed into a more concentrated form mixed with other ingredients or consumed directly, including concentrates, extracts, edibles, oils, tinctures, topicals, and other products. Combusted flower remains the dominant mode of use, but manufactured products have considerable market presence. Among U.S. adult cannabis users in 2014, 7.6% of past-month users and 9.9% of ever-users reported using a vaporizer or other electronic device (though some devices can vaporize dry flower); 16.1% of past-month users and 29.8% of ever-users reported using edibles (Schauer et al. 2016). Among adolescent cannabis users in California in 2016, 82% of past-month users and 72% of lifetime users reported lifetime edible use (Friese, Slater, and Battle 2017). Manufactured cannabis products collectively represented about one-third of 2016 recreational cannabis revenues in Colorado and Washington (National Academies 2017).

Differences from flower in potency, consumption methods, additives, and perceptions of harm present unique regulatory considerations for manufactured cannabis. Users may opt for manufactured cannabis products to avoid negative health effects associated with combustion (Merry Jane 2015; Popova et al. 2017), but manufactured products also present risks. Some vaporized products (e.g., extracts and oils) are similar to e-cigarettes and sometimes use identical hardware (Giroud et al. 2015), likely presenting similar risks, which for e-cigarettes include inhalation of ultrafine particles and chemical additives that can cause cardiovascular and pulmonary effects (Bhatnagar 2016; Canistro et al. 2017; Chun et al. 2017; Pope et al. 2009). High-potency cannabis concentrates may increase risks for dependence, tolerance, and withdrawal (Loflin and Earleywine 2014), and heating these concentrates for inhalation ("dabbing," which can also produce combustion (Wilcox 2016)) can release toxic chemicals including methacrolein and benzene (Meehan-Atrash, Luo, and Strongin 2017). Edibles can be unintentionally overconsumed by adults (Allen et al. 2017) and accidentally consumed by children (Wang et al. 2016a).

There are cross-cutting concerns between manufactured and flower cannabis and between manufacturing and retail venues, but also distinct issues reflected in regulatory structures. In California, CDPH will oversee manufacturing practices, manufacturer licensing, and cannabis packaging and labeling (California Department of Public Health 2017c). CDFA will monitor cultivation and establish a track-and-trace system (California Department of Food and Agriculture 2017b). BCC will regulate retailers, distributors, testing labs, and microbusinesses (small multi-function operations) (Bureau of Cannabis Control 2017).

Because CDPH's regulatory objective is protecting public health, this analysis focuses on elements under CDPH's authority: labeling, packaging, and manufactured product contents. Many concerns regarding manufactured products also apply to combusted or vaporized flower (e.g., potency), but are addressed here within the limits of CDPH's regulatory authority. Due to the limited cannabis-specific evidence base and overlapping public health concerns between cannabis and tobacco, tobacco control best practices are an apt benchmark for evaluating cannabis regulation. We assess CDPH's regulation of cannabis (California Department of Public Health 2017c) using evidence-based best practices derived from tobacco to inform and educate consumers through on-package labeling, prevent exploitative industry packaging and branding tactics, and restrict product formulations that increase risks of misuse, accidental use, and health harms.

Methods

We analyzed CDPH's proposed medical cannabis manufacturing regulations (California Department of Public Health 2017b) and subsequent emergency medical and adult use regulations (California Department of Public Health 2017c) (summarized in Table 1) against public health tobacco control best practices identified by the U.S. Surgeon General (Surgeon General 2014; Surgeon General 2012), WHO Framework Convention on Tobacco Control (FCTC) and implementing guidelines (World Health Organization 2017b; World Health Organization 2013; World Health Organization 2003), and existing interpretive frameworks (Barry and Glantz 2017; Barry and Glantz 2016; Pacula et al. 2014). Best practices were recognized by at least two sources (Table 1, adapted from Barry and Glantz 2017). Additionally, we incorporate comparisons to other jurisdictions' cannabis rules to contrast regulatory options. We recommend improved cannabis regulations in three categories: labeling, packaging, and product formulations.

Table 1. Public health best practices and relevant sections of regulations (adapted from Barry and Glantz 2016).

	Public Health Best Practice	Purpose	Emergency Regulations (California Department of Public Health 2017c)
Inform and Educate Consumers through On-Package Labeling	***Mandatory health warning label*** (Barry & Glantz 2016; Pacula et al. 2014; Surgeon General 2012, 2014; World Health Organization 2003)	Inform consumers; reduce initiation	**§ 40405: Primary Panel Labeling Requirements: All Products** • Minimum 6-point font and "in relation to the size of the primary panel and container" **§ 40408: Informational Panel Labeling Requirements** • Required warnings about children and animals, use while pregnant or breastfeeding, delayed intoxication, and impaired driving • Minimum 6-point font; "in relation to the size of the primary panel and container"; if container is too small, supplemental label with minimum 8-point font **§ 40410: Labeling Restrictions** • Prohibits "[c]ontent that is or designed to be attractive to individuals under the age of 21," including cartoons, imitation of candy packaging or labeling, and "images, characters, or phrases that are popularly used to advertise to children" **§ 40412: Universal Symbol** • Universal symbol for all cannabis products • Minimum size ½" by ½", "printed legibly and conspicuously"
	Warnings cover ≥30% (ideally ≥50%) of primary product panel (Barry and Glantz 2016; Surgeon General 2012, 2014; World Health Organization 2003)	Ensure visibility of warnings to inform consumers	
	Pictorial warnings in addition to text (Barry and Glantz 2016; Surgeon General 2012, 2014; World Health Organization 2003)	Increase visibility and salience of warnings; convey information to low-literacy populations and non-English speakers	
	Rotating health warning content (Surgeon General 2012, 2014; World Health Organization 2003)	Maintain impact and salience of warnings by reducing familiarity	
Require Plain Packaging	***Plain product packaging*** (Pacula et al. 2014; Surgeon General 2012; World Health Organization 2013)	Reduce initiation; eliminate industry use of package design for marketing; enhance effectiveness of warnings; reduce product appeal	**§ 40410: Labeling Restrictions** • Prohibits packaging with "cartoons; [a]ny likeness to images, characters, or phrases that are popularly used to advertise to children; or [a]ny imitation of candy packaging or labeling" **§ 40415: Packaging** • Prohibits imitation of packaging of "products typically marketed to children"
Prohibit Product Formulations that May Increase Health Risks	***Prohibition of harmful additives such as nicotine and alcohol*** (Barry and Glantz 2016; Pacula et al. 2014)	Limit product addictiveness and harms from substance co-use	**§ 40300: Prohibited Products** • For edible products, prohibits alcoholic beverages and use of additives that "increase potency, toxicity or addictive potential," including but not limited to caffeine and nicotine • Prohibits products shaped like humans, animals, insects, or fruit and any product determined to be "attractive to children" **§ 40305: Requirements for Edible Products** • Limits edible manufactured cannabis products to 10 mg THC per serving and 100 mg THC per package **§ 40306: Requirements for Topical Cannabis Products, Concentrates, and Other Cannabis Products** • Limits nonedible adult use manufactured products to 1000 mg THC per package • Limits nonedible medical manufactured products to 2000 mg THC per package
	Prohibition of characterizing flavors, including menthol (Barry and Glantz 2016; Pacula et al. 2014; Surgeon General, 2012, 2014; World Health Organization 2013)	Reduce product attractiveness to minors; reduce behavioral reinforcement effects	
	Restricted product potency (Barry and Glantz 2016; Pacula et al. 2014; Surgeon General, 2014)	Reduce product addictiveness; limit negative health effects	

Results

Inform and educate consumers through on-package labeling

Effective on-package labeling informs consumers and discourages initiation and use (Table 1). Modern labeling requirements are essential components of effective tobacco control (World Health Organization 2013) that should guide cannabis policy.

Require clear primary panel labeling with large coverage and font size thresholds

The regulations (§ 40405(a)) require primary panel labels with text "in relation to the size of the primary panel and container" and minimum six-point font. A separate informational panel label including warnings is not required to appear on the primary panel, but has a similar six-point font requirement (however, if the container is too small for this label, it must be accompanied by a supplemental label in minimum eight-point font) (§ 40408).

The size, prominence, position, and design of health warning labels influence their impact on risk perceptions (Surgeon General 2012; World Health Organization 2013). The FCTC, the widely adopted global tobacco control treaty, requires tobacco health warnings cover at least 30% and ideally 50% or more of a package's principal display area (World Health Organization 2003), a standard associated with higher health knowledge and motivation to quit (Surgeon General 2012; World Health Organization 2013). Increasing label size also improves effectiveness among youth (Hammond 2012). Some countries' warnings occupy 90% of the package (World Health Organization 2017a), and the tobacco industry has opposed larger, more effective warnings (Hiilamo, Crosbie, and Glantz 2014). The regulations' vague "in relation" standard is vulnerable to industry manipulation. Based on the FCTC's impact on tobacco, implementing a minimum 30% (ideally 50%) coverage requirement for cannabis warnings would eliminate ambiguity and likely produce gains in health knowledge and warning effectiveness, potentially reducing demand.

A larger warning label would also permit more prominent font. Minimum six-point font is consistent with Oregon (Oregon Administrative Rules 333-007-0220 (2017)-b), but considerably smaller than Nevada (Nevada Administrative Code § 453A.512 (2017)), which requires front and rear labels with minimum 12-point font (Figure 1, top). A six-point font is challenging to read (Figure 1, bottom) and smaller than the approximately 10-point font suggested by a cannabis industry white paper (Grossman et al. 2017). Requiring minimum 12-point font matches FDA's requirements for most tobacco warnings (21 C.F.R. 1143.3) and parallels the FCTC's requirement that tobacco health warnings be "large, clear, visible and legible" (World Health Organization 2003).

Include rotating health warnings and pictorial warnings

The regulations (§ 40408(a)) mandate textual warnings of hazards for children and animals, use while pregnant

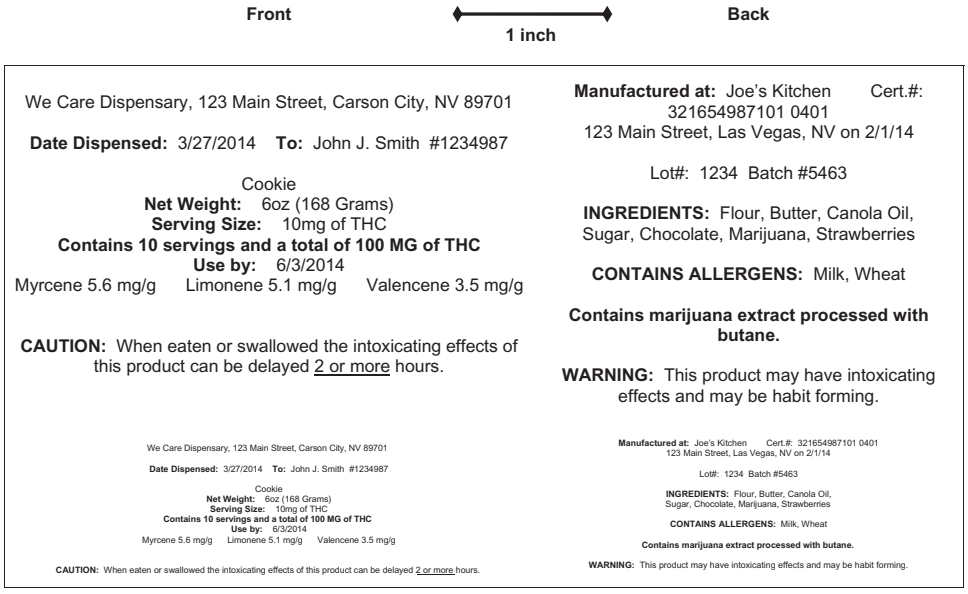

Figure 1. Comparison of 12-point and 6-point label text. (top) Nevada Standard Medical Cannabis Label (Nevada Admin. Code § 453A.512 (2017)) with the required 12-point font. (bottom) The same label with six-point font as required by CDPH regulation § 40405 (California Department of Public Health 2017c).

or breastfeeding, delayed intoxication, and impaired driving. Like the tobacco industry (Hiilamo, Crosbie, and Glantz 2014), cannabis industry stakeholders oppose strong health warnings, deeming them "speculative" and based on "insufficient information" (Grossman et al. 2017). Tobacco warning labels are more effective when changed periodically (Crawford et al. 2002; Hitchman et al. 2014; World Health Organization 2003). To educate consumers and reduce perceptions of harmlessness, cannabis labels should include rotating health warnings consistent with current risk information.

The National Academies Report (National Academies 2017) provides one source for warnings and a corresponding standard for evaluating products' health-related statements, which must be "supported by the totality of publicly available scientific evidence" (§ 40410). On this basis, warnings would include at minimum associations meeting the Report's "Substantial Evidence" standard, including worse respiratory symptoms, problem use and dependence, motor vehicle accidents, lower birth weight, and development of schizophrenia and other psychoses (National Academies 2017). A single standard may be more easily defended against industry pushback. However, ideal warnings would additionally consider evidence from more recent studies, animal studies, and comparable tobacco products to provide more comprehensive risk information regarding secondhand exposure (Wang et al. 2016b), chemical additives (Canistro et al. 2017; Chun et al. 2017), cardiovascular disease (Hall and Weier 2015; Pacher et al. 2017; Thomas and Pollard 2016; Wang et al. 2016b), respiratory disease (Owen, Sutter, and Albertson 2014), neuropsychological decline (Meier et al. 2012), and cancer (California Environmental Protection Agency 2017; Tomar, Beaumont, and Hsieh 2009) based on product type.

Text-only tobacco labels (currently used in the U.S.) are poorly recalled and have low impact on use (Hammond 2011). While not yet implemented by the FDA, the Family Smoking Prevention and Tobacco Act of 2009 requires pictorial health warnings, which are more impactful and informative than text-only warnings (Hammond et al. 2007; Hitchman et al. 2014; World Health Organization 2003) and decrease tobacco product attractiveness to youth (Hammond 2012; McCool et al. 2012). Pictorial warnings are likelier to be seen by low-literacy adults and children and to reach those who cannot read the text language (World Health Organization 2013). Based on demonstrated effectiveness for tobacco, pictorial warnings would likely improve the impact and effectiveness of cannabis labels.

Adopt a highly visible and salient cannabis product symbol

The regulations (§ 40412(a)) require a warning symbol denoting the presence of cannabis. In initially proposed medical regulations (California Department of Public Health 2017b), the symbol referenced psychoactive delta-9-tetrahydrocannabinol (THC) and appeared as an inverted red triangle with "THC" and "!" in white text (Figure 2, left). The emergency regulations (California Department of Public Health 2017c) use a white triangle with a cannabis leaf and "!" in black text and "CA" below the triangle (Figure 2, center).

Tobacco companies' research on packaging color and consumer perceptions indicates that black is most visually prominent, particularly black text on a lighter background (Lempert and Glantz 2016). Red was specified in California's proposed regulations (also Colorado, Oregon, and Washington regulations (Barry & Glantz 2017) and cannabis industry recommendations (Grossman et al. 2017)), but yellow more effectively gains and keeps attention, is perceived as less attractive, and signals a warning, especially with black text as in road signs (Lempert and Glantz 2016). A cannabis warning symbol emulating road warning style, color, and shape (U.S. Department of Transportation 2002) (Figure 2, right) would more effectively attract and maintain consumer attention. A cannabis leaf, as opposed to the more technical "THC,"

Figure 2. Comparison of THC/cannabis warning symbols. (left) Original California THC warning symbol as proposed in CDPH regulation § 40412(a) (California Department of Public Health 2017b). (center) Revised California cannabis warning symbol in emergency CDPH regulations § 40412(a) (California Department of Public Health 2017c). (right) Recommended alternative cannabis warning symbol.

is likelier to be understood by most consumers. Similar visuals appear in Oregon's framework and in industry recommendations (Grossman et al. 2017).

The regulations (§ 40412(b)) require that the symbol be at least one-half inch by one-half inch and "printed legibly and conspicuously." Packaging variation among cannabis products supports mandating coverage of a minimum percentage of the product's primary panel to prevent companies from using large package size, colors, or other markings to render the symbol ineffective. The symbol's size should be considered part of mandatory primary panel warning coverage (at least 30% and ideally 50% of the principal display area based on FCTC tobacco label requirements discussed earlier).

Require plain packaging

The regulations (§ 40415) require cannabis product packaging to be tamper-evident, child-resistant, opaque (for edibles), and re-sealable (for multi-serving products), but do not restrict colors, logos, or branding. Tobacco companies use packaging as a marketing tool to bypass other marketing restrictions (Freeman, Chapman, and Rimmer 2008), establishing brand identification among youth, young adults, and other target populations (Wakefield et al. 2002). The youth marketing effect of package branding is powerful at in-store displays (Robertson et al. 2016), but extends beyond retailers. For example, when an adult purchases a product, children at home will likely see the branded package. For tobacco, WHO recommends (World Health Organization 2003) fully standardized "plain packaging" free of logos, colors, and branding, allowing only plain text brand and variant information in specified size, font, and position (Freeman, Chapman, and Rimmer 2008; Hammond 2014; Tobacco Labelling Resource Centre 2017).

Plain cigarette packaging is associated with reduced brand awareness and identification (Balmford, Borland, and Yong 2016) and reduced cigarette appeal among adolescents and young adults (Germain, Wakefield, and Durkin 2010; Lund and Scheffels 2013; Moodie et al. 2011; White, Williams, and Wakefield 2015). Plain packaging also makes health warnings more noticeable and effective (Beede and Lawson 1992; Surgeon General 2012; Wakefield et al. 2015) and reduces the impact of misleading branding on perceived harmfulness (Wakefield et al. 2015; White, Williams, and Wakefield 2015). Combining plain packaging and large graphic labels extends the reach and impact of public health media campaigns (Brennan et al. 2011) and diminishes tobacco's appeal to adolescents by increasing attention and perceptions of harm and reducing social appeal (McCool et al. 2012).

Cannabis plain packaging examples are limited. Oregon permits cannabis companies using generic packaging and labels to bypass the state's label preapproval process (Oregon Liquor Control Commission 2017a; Oregon Liquor Control Commission 2017b). Uruguay prohibits the two private companies supplying recreational cannabis from including company labels on packaging (Miroff 2017), restricts sales to pharmacies under state monopoly, and does not authorize manufactured cannabis products (Miroff 2017; Pardo 2014, 2017). Under a private commercial cannabis system (as in California), mandatory plain packaging would eliminate a promotional avenue used routinely by the tobacco industry, with likely positive impacts on cannabis use and perceptions of harmfulness.

Eliminate all packaging that appeals to children or imitates non-cannabis products

The regulations (§ 40410(c)) prohibit packaging with cartoons, "images, characters, or phrases that are popularly used to advertise to children," or "imitation of candy packaging or labeling." However, elements not "popularly used to advertise to children" remain appealing to children and teens, including themes of glamour, sex, or adventure. A broader prohibition would better prevent industry targeting of youth. For example, a proposed Canadian recreational cannabis law prohibits packaging and labeling associating a product with "a way of life such as one that includes glamour, recreation, excitement, vitality, risk or daring" or "if there are reasonable grounds to believe that the package or label could be appealing to young persons" (C-45). Even this broader language remains subjective (e.g., defining "glamour"). A plain packaging requirement avoids interpretive problems and removes opportunities to mislead consumers and unlawfully market to youth using packaging.

Absent plain packaging, regulations must anticipate and counter numerous industry tactics. Imitative packaging (copying the appearance of non-cannabis products) is an issue that cannabis industry stakeholders recognize requires regulation (Grossman et al. 2017). The regulations (§§ 40410(c)(3), 40415) prohibit imitating the packaging of "candy" and "products typically marketed to children." This language does not account for the variety of products attractive to children, such as non-candy snack foods (e.g., chips) or products marketed to adults but popular among youth (e.g., granola bars). Regulations should prohibit imitating the packaging of any non-cannabis product to reduce accidental consumption risks and prevent marketing to youth.

Prohibit product formulations that may increase health risks

Evidence of health effects for manufactured cannabis products is even more limited than for cannabis generally (National Academies 2017). Manufactured products also introduce concerns, including additives (California Department of Public Health 2017a, 98), increased potency (Raber, Elzinga, and Kaplan 2015), and similarity to non-cannabis products (Coffman 2014; Leafly 2017).

Clearly prohibit additives that promote addictiveness or initiation, including nicotine, caffeine, menthol, and characterizing flavors

The regulations (§ 40300) prohibit alcoholic beverage infusions and the use of additives that "increase potency, toxicity or addictive potential," such as caffeine and nicotine. CDPH recognizes the risks of tobacco and cannabis co-use and mixing stimulants with cannabis (California Department of Public Health 2017a, 98). The regulations limit these restrictions to edible products (§ 40300) and exclude naturally occurring caffeine (e.g., coffee, chocolate). Regardless of the caffeine's source, such combinations should be prohibited based on risks noted by CDPH. Similarly, nicotine should be prohibited in all forms, including tobacco, e-liquids, and similar products. Crucially, regulations should prohibit harmful additives in all forms of manufactured cannabis products.

Regulations should prohibit adding menthol to non-topical cannabis products. In tobacco products, menthol is more than a flavoring agent, affecting nicotine dependence through behavioral reinforcement (Ahijevych and Garrett 2010) and encouraging breath holding, which increases nicotine exposure (Garten and Falkner 2004). Stimulated by direct and indirect tobacco industry marketing, younger and newer smokers disproportionately use menthol cigarettes, owing to the reduced harshness menthol contributes as a local anesthetic (Rath et al. 2016; Surgeon General 2012). Menthol contributes to the inequitable tobacco burden on the health of African American smokers, who disproportionately smoke menthol cigarettes and have higher rates of tobacco-related diseases despite smoking fewer cigarettes per day and initiating smoking later (Alexander et al. 2016; Yerger 2011). Menthol use is more common among tobacco industry-targeted groups, including youth of color, women, and LGBTQ populations (Giovino et al. 2015). Menthol smokers, especially persons of color and younger smokers, also experience more difficulty quitting (Foulds et al. 2010).

While not direct evidence on the relationship between menthol and cannabis dependence, menthol cigarette smokers are likelier than non-menthol smokers to report past-30-day cannabis use (Kong et al. 2013). Dual use of menthol cigarettes and cannabis also increased from 2005–14 (Schauer et al. 2017). Manufactured cannabis products incorporating menthol already exist (Hughes 2016). Menthol's sensory effects may contribute similar behavioral reinforcement for cannabis as for tobacco, and menthol likely produces similar anesthetizing and cooling effects for inhaled cannabis products as for tobacco. Menthol's links to nicotine addiction and health inequities and associations with cannabis use support a cautious policy prohibiting menthol in non-topical cannabis products to prevent repeating harms attributable to mentholated tobacco products.

Beyond menthol, a prohibition on characterizing flavors in nonedible products is necessary to discourage inappropriate use of medical products and deter youth use. Flavored products attract young smokers to tobacco (Carpenter et al. 2005; Surgeon General 2012; Villanti et al. 2017) and e-cigarettes (Kong et al. 2015; McDonald and Ling 2015). Most adolescent tobacco and e-cigarette users' use is initiated with flavored products (Ambrose et al. 2015). Disguising unpleasant tastes with flavors to attract young users is a tobacco industry strategy the cannabis industry could employ, absent strong regulations.

The FDA's 2009 ban on cigarettes with characterizing flavors precipitated a decrease in adolescent tobacco use and substantial reductions in the probability of being a cigarette smoker and in cigarettes smoked among adolescents (Courtemanche, Palmer, and Pesko 2017). Because the final 2009 ban failed to include menthol cigarettes or flavored non-cigarette tobacco, increased use of cigars, pipes, and menthol cigarettes (implying substitution for flavored cigarettes) limited the impact on adolescent tobacco use (Courtemanche, Palmer, and Pesko 2017). Cannabis regulations should prevent similar effects by prohibiting characterizing flavors in nonedible products. Flavored edibles present similar concerns requiring further research on impacts on use and initiation. Regarding medical cannabis products, any therapeutic effect is likely unrelated to flavorings, and alternative formulations should remain available.

Set lower THC limits for inhaled products compared to other nonedible products

The regulations (§ 40306) limit nonedible manufactured cannabis products to 1000 mg (adult use) or 2000 mg (medical) THC per package, far higher than the 100 mg permitted for edibles (§ 40305), to balance

accidental consumption risks against patient access concerns. CDPH noted that "capsules, tinctures, and topicals" are "more traditional medical delivery mechanisms" (California Department of Public Health 2017a, 102), but nonedible products is a broad category that includes highly potent concentrates that can be heated and quickly inhaled (Raber, Elzinga, and Kaplan 2015), providing the THC equivalent of several joints in one breath (Miller, Stogner, and Miller 2016). Such products potentially present increased dependence risks (Loflin and Earleywine 2014) and have been linked to psychosis (Pierre, Gandal, and Son 2016).

Other inhalable manufactured products that are less concentrated or consumed more slowly also present risks. Vaporizing liquid extracts causes inhalation of ultrafine particles, which present cardiovascular and respiratory risks in e-cigarettes (Bhatnagar 2016; Canistro et al. 2017; Chun et al. 2017; Pope et al. 2009), and likely have similar risks for vaporized cannabis products. Based on combustion's health risks, harm reduction strategies might favor policy preference for non-smoked over smoked cannabis (Budney, Sargent, and Lee 2015; Fischer et al. 2017), but other risks support disfavoring all inhaled cannabis products, combusted or vaporized. Alongside other strategies (e.g., comprehensive smokefree policies, public education campaigns), a restrictive THC limit for inhaled products may move consumer choice away from such products. In contrast, policy promotion of inhaled products, especially as medicine, by allowing higher THC content may contribute to existing trends toward renormalization of smoking behaviors (Budney, Sargent, and Lee 2015), diminished perceptions of cannabis harmfulness (Keyes et al. 2016), and the "pharmaceuticalization" of cannabis and nicotine products (Hendlin, Elias, and Ling 2017).

A 100 mg THC per unit limit on all inhaled manufactured cannabis products (matching that for edibles) would better protect public health and denormalization of smoking behavior, while maintaining access to other (non-inhaled) higher-potency products based on medical need. Similar potency concerns apply to smoked and vaporized flower, but are outside the scope of this analysis.

Set lower THC limits for manufactured products likely to be accidentally consumed

The regulations (§ 40305) limit edible products to 100 mg THC per package, based on CDPH's survey of other states and the adult use limit set by ballot initiative (California Department of Public Health 2017a, 100–102)). Washington (Washington Administrative Code § 246-70-040) and Oregon (Oregon Administrative Rules 333-007-0220 (2017)-b) also limit medical edibles to 100 mg, while Oregon restricts adult use edibles to 50 mg (Oregon Administrative Rules 333-007-0220 (2017-a). Colorado established a 100 mg adult use limit (1 Colorado Code of Regulations § 212-2: R 103) in response to highly publicized overconsumption incidents (Barrus et al. 2016; Subritzky, Lenton, and Pettigrew 2016). Acute THC overconsumption can cause panic attacks, paranoia, hallucinations, and impaired motor function and may contribute to accidental deaths, while pediatric exposure can cause respiratory failure, coma, and serious cardiovascular symptoms (National Academies 2017, 53, 231–234). A 50 mg per package THC limit for adult use edibles would reduce the risks of pediatric consumption by limiting the amount easily consumed.

Edible products present clear accidental consumption risks due to similarity to non-cannabis products and were responsible for approximately half of pediatric cannabis exposures in a two-year Colorado study (Wang et al. 2016a). CDPH addressed this risk by prohibiting products shaped like humans, animals, insects, or fruit and products CDPH determines are "attractive to children" or "easily confused with commercially available foods" (§§ 40300(j)-(l)). However, nonedible products also present accidental consumption risks. Non-cannabis topical products account for 5.3% of pediatric exposure calls to poison centers nationally (Mowry et al. 2016), and cannabis-infused products add additional risks, especially those resembling products children commonly encounter, such as lotions (Leafly 2017). While most cannabis topicals are not psychoactive when used properly, accidental ingestion remains concerning. Many concentrates and extracts resemble food (e.g., honey (Abad-Santos 2013)) or trade on food-like flavors or aromas (e.g., "Pineapple Dream Concentrate" (Goncus 2016)). Harmful pediatric exposures to e-cigarette and nicotine liquids are increasingly frequent (Kamboj et al. 2016), and similar preparations of cannabis extracts could present related risks. We recommend extending the 100 mg THC per package limit for edibles to nonedible manufactured cannabis products with significant accidental consumption risks, including concentrates, extracts, and topicals.

A higher threshold for more traditional medical products (e.g., capsules, tinctures, and patches), as intended by the original proposed regulations (California Department of Public Health 2017a, 102), appropriately balances patient needs and public health risks. However, the 2000 mg limit for nonedible medical products (§ 40306) is higher than states such as

Washington, which limits "High THC compliant products" (capsules, tablets, tinctures, transdermal patches, and suppositories) to 500 mg THC per package and limits all other products to 100 mg (Washington Administrative Code § 246-70-040). In contrast, Oregon allows nonedible and nontopical medical manufactured cannabis products to contain up to 4,000 mg THC (Oregon Administrative Rules 333-007-0220 (2017b). Given the lack of evidence on appropriate dosages, medical utility, and health risks for manufactured cannabis products, a lower threshold presents fewer risks.

Discussion

State cannabis legalization and regulation, despite continued federal illegality, represent a massive shift in regulatory approach. While there are probable benefits, notably potential medical utility for some conditions (National Academies 2017) and ending discriminatory criminal enforcement practices (Bender 2016), legalization also brings substantial public health risks similar to tobacco. The creation and government endorsement of a legal cannabis industry may allow large corporations to dominate markets (Barry, Hiilamo, and Glantz 2014) and increase demand while exerting powerful influence over the regulatory environment, as tobacco and other industries have done (Barry and Glantz 2016; Richter and Levy 2014; Subritzky, Lenton, and Pettigrew 2016). Protecting public health requires well-controlled cannabis markets to minimize use, diversion, and development of a powerful industry working to maximize consumption (and profits) at the expense of public health.

Evidence for cannabis's negative health effects (and medical efficacy) is underdeveloped due to longstanding research barriers (Hudak and Wallack 2015; National Academies 2017). However, evidence of health harms, including respiratory (National Academies 2017), cardiovascular (Pacher et al. 2017), cerebrovascular (Yankey et al. 2017), psychological and mental health (Hasin et al. 2012; Sewell, Poling, and Sofuoglu 2009), cancer (California Environmental Protection Agency 2017; Tomar, Beaumont, and Hsieh 2009), injury risks (National Academies 2017), among other concerns, supports a precautionary approach.

Cannabis is not tobacco, and the cannabis industry is not, for now (Barry, Hiilamo, and Glantz 2014), the tobacco industry. Nevertheless, cannabis has health risks, many analogous to tobacco, and much remains unknown about the health effects of manufactured cannabis products. A precautionary approach, informed by evidence-based tobacco control best practices, will minimize potential population health harms and avoid repetition of dangerous tobacco industry behavior by the cannabis industry.

The tobacco industry has opposed effective and innovative public health policies to prevent regulatory diffusion (Hiilamo, Crosbie, and Glantz 2014). California's size, economy, and status as a leading cannabis producer make the state's cannabis regulation vital to public health and likely to influence other states' frameworks. California's cannabis manufacturing regulations recognize the importance of warning labels, restricting packaging, prohibiting addictive additives, and controlling potency, but fall short in preventing repetition of tobacco industry practices. Larger, more effective warnings, plain packaging, and stricter limits on product constituents and potency would help inform consumers, inhibit harmful marketing practices, and improve product safety.

Limitations

The short history of legal cannabis markets limits direct evidence of the impact of cannabis regulations. Medical cannabis legalization in the U.S. dates only to 1996, with most states that have legalized medical cannabis doing so after 2010. Markets in many early adopting states, including California, were loosely regulated. Cross-jurisdictional comparisons are complicated by cannabis's complex legal status (Pacula et al. 2002). The history of adult use legalization is shorter, beginning in 2012. The lack of cannabis-specific evidence supports using tobacco control as a regulatory model. If additional evidence demonstrates meaningful differences in health effects or other relevant factors, this could reduce tobacco control's utility as a cannabis regulation model.

Our potency recommendations are limited by THC dosage complexity. A typical joint contains 8–13 mg THC; while frequent users may develop tolerance, occasional users may experience a "high" at just 2–3 mg (Hall and Pacula 2010; National Academies 2017). Typical medicinal dosage may range from 1–120 mg THC daily, depending on condition and tolerance (Mayo Clinic 2013). Route of administration strongly influences cannabis pharmacokinetics, and individual variability is high (Barrus et al. 2016). Other cannabinoids (e.g., cannabidiol (CBD)) and compounds (e.g., terpenes) may also modulate THC's psychoactivity, a phenomenon known as "entourage effects" (Russo 2011). Such effects would make direct dosage comparisons between THC-only pharmaceutical products (e.g., Marinol®) and those

with more complex chemical profiles inaccurate, rendering regulations based solely on THC content incomplete. However, while CBD is pharmacologically active but non-intoxicating (National Academies 2017), overall evidence for entourage effects remains limited and controversial (Chen 2017). The current limited evidence base dictates that specific cannabinoid thresholds should be continually reviewed on a set schedule to ensure consistency with the best available evidence.

Finally, the withdrawal of the proposed medical regulations in July 2017 and the emergency basis of the November 2017 regulations mean specific regulatory text referred to may not reflect final regulations. While the emergency regulations will be implemented, they will be followed by public comment and potential subsequent CDPH revisions.

Conclusion

CDPH's cannabis regulations recognize the need to protect public health, but prioritizing public health over business interests requires a more assertive approach to labeling, packaging, and product formulation. Requiring large and proportionate warning labels, a visually prominent universal cannabis symbol, and rotating health warnings incorporating pictorial content would reduce appeal to minors and better inform adult consumers. Prohibiting all imitative packaging and, ideally, requiring plain packaging would increase warning efficacy and curtail harmful industry behavior that uses packaging as a marketing tool. Comprehensively prohibiting additives that promote addictiveness or initiation, including menthol and other characterizing flavors, would discourage inappropriate use of medical products and limit initiation. Limiting potency for inhalable products and those easily confused with non-cannabis products would mitigate dependence, abuse, and accidental use risks.

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