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Testing for Psychoactive Agents

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BACK OF THE ENVELOPE CALCULATIONS

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Outline

Cannabinoid potency testing is potentially valuable to consumers and the wider public, but it comes at a cost. These costs and benefits will vary according to the type, accuracy, and comprehensibility of the information presented to consumers. Designing potency testing rules therefore requires a balancing act.

There are two mechanisms for achieving this balance: state regulation and market competition. In the medical marijuana market, for example, laboratories offer marijuana producers and retailers a wide range of potency tests, varying by methodology, accuracy, comprehensiveness, and price. Under such a *laissez faire* approach, the role of the state is limited to ensuring the honesty of marketing claims, according to generic truth-in-advertising laws.

This paper assumes that rigorous potency testing rules are appropriate in the commercial cannabis market for the same reasons they are necessary in the alcohol market: drugs pose special risks to consumers, can result in addiction and other disorders that undermine rational decision-making, and impose external costs on society at large. These costs can be mitigated by testing the content of products sold on the I-502 market, and using the test results to either prohibit certain products from market or to simply convey that information to the consumer as to improve his ability to make wise choices.

There are diminishing returns on the rigidity and comprehensiveness of testing regulations. The more obvious aspect is that regulations can make the marijuana supply-chain more complicated and costly. Simple economic theory suggests that the price of any required testing procedures will be passed on to consumers in the form of higher prices. In the specific case of the Initiative 502 market, this may threaten the viability of the regulated market and its ability to compete on price with the parallel black and medical markets.

Less obviously, not all information about the chemical components of marijuana is equally useful to the consumer. On one hand, there are many ways to measure the chemical content of a package of marijuana, but relatively few of those metrics are relevant to user experience, health, and safety. On the other hand, there are limits to the consumer's attention and psychopharmacological literacy. That concern argues for selectively choosing those chemical measurements required to appear on the retail label. A simple and elegant label gives consumers better chances of noticing, understanding, and reacting appropriately.

This paper explores the issues that arise in determining this balance. It draws upon peer-reviewed journals, popular wisdom, and commercial cannabis testing laboratories to address what to test for; how accurate such tests should be; how such tests should be conducted and reported; and how much testing will cost.

The first four chapters of this paper address these questions, while the fifth concludes with a summary. Each section is briefly described below.

I. Which Cannabinoids to Count?

The first issue for consideration in designing potency testing rules is this: which cannabinoids do we need to count? The vast majority of the over 95 known cannabinoids are either poorly understood, not linked with significant effects, or rarely present in meaningful quantities. For these cannabinoids, the consumer is unlikely to benefit from knowing their concentrations. Worse still, requiring such information on the label might distract the consumer from information on more relevant cannabinoids. Finally, for most of these cannabinoids, quality control testing laboratories lack the materials needed to perform accurate and precise quantitative testing.

II. Bioavailability and Implications for Testing Accuracy

Potency testing is intended to help consumers monitor and control their intake of cannabinoids, and to prevent accidental overdose. Due to the biological heterogeneity among cannabis users, and the resulting variable pharmacokinetics of cannabis, it may not be useful for potency tests to achieve high degrees of accuracy. There appears to be substantial variability in the bioavailability and subjective effects of the major cannabinoids, even when an identical product is used in an identical way, both from one person to another and for the same person across multiple sessions of use. This section reviews the scientific literature on the pharmacokinetics of cannabinoids when smoked, vaporized, ingested orally, absorbed sublingually, and applied topically, and discusses the implications for the usefulness of precision in potency tests.

III. Testing and Labeling Practices

Product labels play an integral role in conveying the results of potency tests to consumers. Labels should be both accurate and comprehensible. This section discusses the complications of testing and labeling for cannabinoids, including the different methods of cannabinoid quantification; the distinction between testing usable marijuana and testing marijuana-infused products; the challenges in quantifying minor cannabinoids without certified chemical standards; and the care that needs to be taken in THC and THCA quantification.

IV. The Costs of Cannabinoid Analysis

Requirements for potency testing should aspire to minimize the cost burden on the I-502 market. This section reviews the factors that contribute to testing costs; the testing costs observed across different laboratories; and the anticipated cost burden of testing as a proportion of cannabis product value.

V. Conclusion

Finally, the paper draws together the findings of the above four sections and discusses implications for specific policy decisions.

I. Which Cannabinoids to Count?

This section first identifies the cannabinoids that testing laboratories, pharmaceutical companies, and popular wisdom suggest are worth further attention (Section A), and then explores the peer-reviewed scientific literature on these compounds to assess which have psychoactive effects significant enough to warrant the consumer's attention (Section B).

A. Common cannabinoids in potency testing and conventional wisdom

Cannabis chemistry is extremely complex, with at least 95 distinct cannabinoids (Poklis, 2010), 200 terpenoids (Russo, 2011) and 20 flavonoids (Partland, 2002) identified in plant material.

The cannabinoids are a class of compounds that activate cannabinoid receptors within the body. The cannabinoids discussed within this paper are unique to the cannabis plant, but some cannabinoid-like compounds, such as beta-carotene, are commonly found in plants and foods.

Terpenes are not unique to cannabis but are a large class of compounds found throughout the plant kingdom. Of the terpenes found in cannabis, some of the most common are myrcene, linalool, alpha-pinene, caryophyllene, and limonene, which are found in mangos, lavender, evergreen trees, black pepper or cloves, and citrus fruits respectively. Many terpenes are known to be physiologically active, and some of the terpenes in cannabis even interact with the CB2 receptor in the endocannabinoid system.

Flavonoids too are found throughout the plant kingdom. Cannabis plants include common flavonoids, such as apigenin, while others like the cannaflavins are unique to cannabis (Partland, 2002). Like the terpenes, some flavonoids are thought to influence the subjective experience of consuming cannabis.

Of all these, which should be included on a potency label? To begin narrowing this list of compounds, it is instructive to consider the following:

1. Which compounds are reported in cannabis-based medical products
2. Which compounds are routinely tested for by existing laboratories
3. Which compounds have certified standards available to allow reliable testing

Medical Products: Sativex

Sativex is a patented oromucosal spray developed by GW Pharmaceuticals, marketed for medicinal purposes. The following 13 cannabinoids are routinely detected in Sativex (Guy, 2005):

- Delta-9-tetrahydrocannabinol (Δ9-THC), approximately 40% of the content of Sativex;
- Cannabidiol (CBD), approximately 35% of the content of Sativex;

- Minor cannabinoids, including: Cannabichromene (CBC), Cannabigerol (CBG), Cannabinol (CBN), Tetrahydrocannabivarin (THC-V), Cannabidivarin (CBD-V), Tetrahydrocannabinolic acid (THCA), Cannabidiolic acid (CBDA), Cannabicyclol (CBL), Cannabitriol (CBO), Cannabielsoin (CBE), and Cannabichromivarin (CBC-V);
- 9 terpenes and a range of other compounds, including fatty acids, sterols, carotenoids and flavonoids

It is important to note that in Sativex, only Δ9-THC and CBD are quantified or discussed in relation to its medical efficacy. The other 11 cannabinoids and various other chemicals are noted as 'present', but not quantified or labeled on the final product.

Current Testing Practices

Nearly all cannabis testing laboratories test for three cannabinoids: THC, CBD, and CBN. Additionally, laboratories using high performance liquid chromatography (HPLC) equipment test for THCA, and often for CBDA. A number of laboratories claim to test for minor cannabinoids, some of which lack commercially available testing standards. Terpene analysis is very rare, largely due to low levels of consumer interest and scientific information about their effects.

Availability of Testing Standards

To accurately quantify cannabinoid content, laboratories require access to a certified chemical standard for each cannabinoid. A chemical standard is a purified solid or solution of a specific chemical of known concentration, supplied by a chemical company with a certificate of analysis. For example several cannabinoids can be purchased from scientific supply companies in sealed vials at 1.000 milligram per milliliter. In laboratory tests, these chemical standards are used to calibrate equipment so that tests are accurate. At present, availability for these compounds is limited to THCA, Δ9-THC, Δ8-THC, CBC, CBG, CBN, and CBD (RESTEK, 2013). CBDA is not available at the time of writing.

Some labs attempt to quantify cannabinoids beyond this list using in-house standards. These standards have not been independently verified, typically differ between laboratories, and are not usually supported by an independent certificate of analysis, so carry risk of low inter-laboratory accuracy and precision. As demand for these minor cannabinoids grows, and as the science evolves, scientific supply companies may produce chemical standards for more cannabinoids so reliable quantification can be done routinely.

Standards are commercially available for the common terpenes, but there is a similar lack of chemical standards for rarer terpenes.

B. Review of selected cannabinoids

This section reviews the current scientific opinion on cannabinoid significance. Of the cannabinoids and terpenes identified in Section A, scientific journals suggest that only six have established psychoactive and/or medical significance: the cannabinoids THCA, THC,

CBD, CBDA, CBN and Δ8-THC. Below, we discuss each of these cannabinoids in detail, including typical concentrations within cannabis flower, psychoactivity and health impacts, and any implications for potency labels.

Other candidates for consideration were CBC (recorded to have some effects including anti-depressive) (El-Alfy, 2010), CBG (which interacts with a range of receptors and holds promise for several diseases), and THC-V (a CB1 and CB2 antagonist with promise for anti-inflammatory, anti-obesity, anti-convulsant, anorectic and pro-bone growth effects (Izzo, 2009)). However, the scientific literature on these compounds has not demonstrated significance from a regulatory perspective, although further study might reveal new implications. Nonetheless, some consumers may value marijuana containing these chemicals, perhaps due to fashions or emerging evidence of psychoactive or medical effects.

Finally, the terpenes and flavonoids were considered. In popular wisdom, different strains of cannabis are thought to produce distinct experiences, even where cannabinoid content is identical. Emerging research suggests that this may be due to the distinct terpene and flavonoid profiles of different cannabis strains. One study examines the terpene profiles of the strains "White Widow" and "Amnesia", and finds that high levels of myrcene, a terpene linked to sedation, may account for the 'couch lock' effect associated with White Widow, while low levels of α-pinene, a terpene linked to memory effects, may account for the short-term memory loss associated with the Amnesia cultivar (Hazekamp, 2012).

Because the terpene profile of a given cannabis cultivar appears to be expressed reliably between plants, it may be possible to 'fingerprint' cannabis varieties. This would allow consumers who learn that they prefer a specific cannabis cultivar to seek out products where the strain has been verified as genuine. The technical challenges associated with terpene profiling are considered further in Section 3.

Nonetheless, scientific knowledge on the role of *specific* terpenes in the psychoactivity of cannabis remains in its infancy. As such, no terpenes are individually considered in this section, and no terpene warrants mandatory reporting on cannabis product labels.

THCA (aka Δ9-THCA or Tetrahydrocannabinolic Acid):

Typical concentration

In raw, fresh plant material, THC-A represents the vast majority (80 – 99%) of total THC . (Total THC is a term frequently used on cannabis labels in the gray market, as a convenient term to describe the combination of psychoactive THC molecules and not-yet psychoactive THC-A molecules.) As cannabis decays over time or is subjected to heat, THC-A is broken down into THC by a process called decarboxylation. Accordingly, marijuana eaten raw is only mildly psychoactive. Popular methods of ingesting marijuana can also be viewed as convenient methods of decarboxylation, including smoking, cooking, and vaporization. So while usable marijuana might regularly contain between 5 and 20% THC-A, infused marijuana products are intended to contain none at all. (However, sloppy infusion processes can result in incomplete decarboxylation, "wasting" the cannabinoids that will be ingested by the consumer in relatively non-psychoactive forms.)

The rate at which decarboxylation converts THC-A to THC is variable and less than 100% efficient. Even under ideal temperature conditions, the end product (THC) represents at most a 70% conversion of the original THC-A, and the remainder breaks down into a number of other insignificant byproducts.

Psychoactivity

THCA is not known to be psychoactive, except indirectly as the precursor to THC. When THCA is ingested prior to heating, it does not yield psychoactive effects until metabolic processes convert the chemical to THC; even then, rates of conversion to THC after ingestion are limited (Jung, 2009).

Medical significance

It is unclear whether THCA delivers medical benefits. Suspected effects include steroid interactions (Wantanabe, 2005), immune system modulation (with possible positive effects on autoimmune disorders) (Verhoeckx, 2006), anti-inflammatory effects (Ruhaak, 2011) and neuroprotective effects (Moldzio, 2012).

Policy implications

THC-A is of variable significance: crucial for raw usable marijuana but only secondarily important for decarboxylated marijuana-infused products.

When testing raw usable marijuana, THC-A levels are the strongest indicator of the sample's psychoactive potential (Zeeuw, 1972). This is problematic: laboratories are unable to directly measure the outcome of interest (THC). It is common practice among testing labs to convert THC-A levels into a "total mg THC" that is representative of a 100% conversion of THCA to THC based on molecular weight. (For further discussion of complexities in using this label appropriately, see section 3B on Labeling).

Not all marijuana is intended to be decarboxylated before ingesting. Due to THC-A's purported health benefits, some consumers prefer to eat raw marijuana leaves, and others prefer to juice it into a beverage or extract it into a concentrate. (The second type of products may be marketed as "high THCA".) These types of carboxylated marijuana-infused products present two unique challenges: (1) Over time, THCA content will degrade into THC, such that a non-psychoactive product could gradually become psychoactive; (2) Uninformed consumers may be unable to understand that the product is both non-psychoactive if consumed cold (unlike an edible) and highly psychoactive if vaporized or cooked.

Another reason for drawing attention to THC-A in marijuana-infused products is the possibility of products 'spiked' with THC-A, intended for decarboxylation by the user but only labeled with their carboxylated psychoactive content. For example, consider a container of frozen cookie dough balls, each containing 10mg THC as required by the Board, but also containing 40mg THCA. There could be an instruction on the package that these cookies really 'pop' after baking them. Once cooked, the cookies could contain a full 30-40mg of THC each.

The problem of partially decarboxylated marijuana-infused products could be addressed by at least two alternatives. One approach could be to prohibit such products on the recreational market, requiring that extracts and edibles are fully decarboxylated (i.e. all THCA transformed into THC) prior to sale. Alternately, if these products are to be allowed, their labels might warrant additional text disclaiming that potency might change over time and method of use.

THC (aka Δ9-THC, Δ9-Tetrahydrocannabinol or Δ1-THC):

Typical concentration

In raw plant material, THC is scarce and comprises only a small minority (between 1 and 20%, by weight) of the sum of THC and THC-A. In decarboxylated material, THC levels range from as low as less than 1% to as much as 30%, with a US average of 8.8% and a California average of 12% THC in 2008 (Burgdorf, 2011; Mehmedic, 2010; Hardwick, 2008). The low end of this range would be considered hemp; the middle of the range is typically filled with lower quality marijuana, bred outdoors and at low costs; the high end of this range is dominated by sinsemilla.

Psychoactivity

THC is the principal psychoactive component of cannabis and acts upon a range of receptors, notably CB1 and CB2 (Futoshi, 2005). Once ingested, THC can be metabolized in several different ways, depending in part on the mode of ingestion. For instance, when ingested orally, THC is metabolized by the liver into 11-Hydroxy Δ9 THC (or 11-OH Δ9 THC) at distinctively high rates. 11-OH-Δ9-THC has similar but perhaps more potent psychoactive effects than THC, and after oral ingestion can appear in concentrations higher than THC, likely becoming the dominant source of psychoactivity.

Medical significance

THC has been proven to have high medical potential for the treatment of nausea (Futoshi, 2005), pain (Guy, 2005), various symptoms of muscular sclerosis (Guy, 2005), depression (El-Alfy, 2010), and many more conditions. It is also associated with negative mental health impacts, including anxiety, memory deficits, and schizophrenia, although in the latter case causality remains unresolved (McLaren, 2010).

Policy implications

THC's role as the primary psychoactive agent is undisputed by both scientific literature and popular culture. Common practice among testing laboratories is to include THC under a 'Total % THC' label in useable cannabis, and a 'Total mg THC' label in edibles. In many access points and dispensaries, '% THC' is the only potency metric marketed at the retail counter. (This is an imperfect system, since consumers may not easily relate mg THC to a volume of marijuana-infused product labeled with a Total THC percentage – the introduction of a standard "serving size" or "dosage unit" can ameliorate this difficulty.)

CBDA (aka Cannabidiolic acid)

Typical concentrations

CBD and CBD-A share the same relationship as do THC and THC-A. CBD occurs at very low levels in raw cannabis, roughly ten percent of its levels in decarboxylated product.

Psychoactivity

CBDA has no known psychoactive effects or interactions.

Medical significance

CBDA does not activate CB1 or CB2 receptors and has negligible effects against multiple cancers (McAllister, 2007). It has significant anti-inflammatory properties (Takeda, 2008), reportedly more so than all other minor cannabinoids. CBD-A has no direct psychoactive effects; however, it has a potential for decarboxylating into CBD (see below).

Policy implications

CBD-A is important for many of the same reasons as THC-A; one important difference is that fewer, if any, consumers ingest carboxylated CBD-A for medicinal purposes. (However, such practices could become popular in the future; trends or fads in popular health are volatile and difficult to predict, regardless of a practice's proven health benefits or lack thereof.)

In raw plant material, CBD-A is a useful proxy for CBD levels post-decarboxylation. For usable marijuana, common practice among laboratories is to combine CBD and CBD-A levels and report them as 'Total mg CBD.' Decarboxylated marijuana-infused products typically contain no CBD-A, unless they have been only incompletely decarboxylated due to poor producer techniques.

There is no accepted chemical standard for quantifying CBD-A; participating laboratories generally use an in-house standard. Accordingly, CBD-A quantifications may be inconsistent across different laboratories until a standard is developed and made available to I-502 laboratories. Until then, the lack of a chemical standard would complicate a requirement for CBD-A to appear on potency labels. Other labs will decarboxylate a sample and report the resultant CBD level; however this is a far from perfect procedure.

CBD (aka Cannabidiol):

Typical concentrations

CBD typically appears at much lower levels than THC; in recent years, breeding strategies aiming to maximize THC may have exacerbated this pattern. Because THC and CBD compete for synthetic pathways within the cannabis plant, breeding strategies typically seek either to maximize THC, to maximize CBD, or to obtain a particular ratio. It is not possible, however, to maximize both.

Samples from California indicate an average CBD level close to 0.1% in 2008, with a minimum of zero and a maximum of 0.5%. Average CBD content was closer to 0.3% around the year 2000 (Burgdorf, 2011). In rare cases, levels of CBD in cannabis can reach more than 3% (Hardwick, 2008), although this is more typical in strains bred for their CBD concentrations. There are a number of high CBD strains that exceed 10%, or reportedly even as high as 17% CBD.

The ratio of CBD to THC is considered a useful indicator of a strain's psychoactive effects, due to interactions between the two compounds. The commercial medical preparation Sativex contains a near 1:1 ratio of CBD to THC (Karschner, 2011). Among samples gathered in a University College London study, average ratios of CBD to THC ranged from 0.02 in sinsemilla to 0.53 in some resins (Morgan, 2010).

Psychoactivity

The data on CBD psychoactivity is complex. It has no marked psychoactivity in and of itself, but it is purported to moderate many of the effects of THC. (Cannabis consumers tend to prefer low-CBD strains over high-CBD strains, perhaps for this reason (Morgan, 2010).) CBD appears to reduce anxiety associated with THC, possibly by blocking THC from binding to CB2 receptors (making it an inverse agonist) (Mechoulam, 2007; Pertwee, 2008). This interaction may explain an apparently lower rate of psychotic episodes for consumers using high-CBD cannabis (Schubart, 2011), as well as how CBD mitigates THC's negative effects on memory (Fadda, 2004). CBD may also block the formation of 11-OH-THC (a powerful psychoactive metabolite of THC) in the liver, but there is controversy over whether CBD alters the pharmacokinetics (how the body interacts with the chemical) of THC (Huestis, 2007).

Medical significance

CBD is often regarded as the most medically promising cannabinoid. It has shown promise as a treatment for a range of disorders and diseases, including cancer (McAllister, 2007), multiple sclerosis, schizophrenia (Morgan, 2008), addiction (Morgan, 2010), and epilepsy. It has been claimed to have anti-psychotic, anti-hyperalgesic, anti-convulsant, neuroprotective, anti-ischemic (Mechoulam, 2007), anti-emetic (Parker, 2011), anti-depressive, and anti-proliferative effects.

Policy implications

Next to THC, CBD is perhaps the most commonly known and advertised cannabinoid. However, it is a far second. Current evidence suggests that that CBD mitigates some of the negative public health impacts of cannabis. Accordingly, there is a public interest in encouraging popular awareness of CBD and fostering demand for products with a lower THC:CBD ratio.

This logic suggests requiring CBD potency labels on all cannabis products, even those without CBD content. Another educational option is to distinguish marijuana that meets a minimum THC : CBD ratio (e.g. a "CBD balanced" label). It may also be helpful to provide accompanying documentation informing consumers about CBD's potential to lessen THC-induced anxiety and other negative side effects.

CBN (aka Cannabinol):

Typical concentrations

CBN is a degradation byproduct of Δ9-THC. In gray and black market cannabis, it is usually found at levels below 1%. The ratio between THC and CBN is sometimes used to date stored marijuana samples, according to the same logic as carbon dating (Flemming, 2007).

Psychoactivity

CBN is a weak CB1 and CB2 agonist, triggering the same receptors but with approximately 10% of the activity of Δ9 THC (Hosking, 2008). Conventional wisdom among cannabis consumers links CBN to drowsiness (Legal Marijuana Dispensary, 2013).

Medical significance

CBN may have some immune modulation effects via the CB2 receptor (Jan, 2002; Herring, 1998) and some potential as a treatment for multiple sclerosis and glaucoma (Weydt, 2005; Colasanti, 1984; ElSohly, 1981). It may react with other receptors besides CB1 and CB2, but these have yet to be intensively studied.

Policy implications

CBN is sometimes used in popular culture as an indicator of cannabis freshness, due to its role as a breakdown product of THC. According to that logic, a fresh product will have low levels of CBN, but a product that has been stored improperly or for too long will show a significant portion of its THC deteriorated into CBN. However, this method of dating may mislead the customer if the test results are old, or if cannabis has been improperly stored, for instance by exposure to sunlight or warm temperatures. An alternative approach is to place time stamps on product labels, indicating the date of testing, packaging, or other events within the supply chain.

Contrary to the practice of some labs, CBN should not be used to calculate 'Total mg THC.' According to a rough calculation as discussed above, it may take as many as roughly seven milligrams of CBN to deliver the same psychoactive effect as one milligram of THC. Simply summing their weight and marketing that total as 'Total mg THC' would tend to overstate potency. While THCA may eventually convert into THC, CBN will never revert into THC.

In summation, CBN's relative scarcity and mild psychoactive effects suggests that it need not appear on potency labels. Moreover, its presence on the product label could contribute to crowding, and therefore distract the consumer from chemicals with more significant effects, such as THC and CBD. If CBN levels are to be reported on the label, label design should encourage the consumer to think of CBN as an indicator of freshness rather than overall potency. This may be achieved by visually distinguishing CBN from THC and CBD, the primary indicators of potency, perhaps by declaring CBN in smaller text or under a different heading.

Δ8-THC (aka Δ8-tetrahydrocannabinol)

Typical concentrations

Δ8-THC is typically found at very low levels, well under 1%.

Psychoactivity

Δ8-THC exhibits lower psychotropic potency than Δ9-THC, and has been referred to as possessing 'half' the potency (Abrahamov, 1995).

Medical significance

Δ8-THC possesses antiemetic, anxiolytic, appetite-stimulating, analgesic, and neuroprotective properties (National Cancer Institute).

Policy implications

Δ8-THC likely need not appear on potency labels, for the same reasons as apply to CBN. It should not be included in any 'total THC' claims due to its scarcity and low efficacy per weight.

Section I Conclusion: Implications for testing

In the process of reviewing of psychoactive agents in cannabis, we have identified a few principles universal to all chemicals. These concepts apply equally to several chemicals.

Handling decarboxylation, whether intentional or accidental.

THC-A and CBD-A have completely different effects than THC and CBD; typically, carboxylated (raw) intake is for medical intent, and decarboxylated (smoked, cooked, or vaporized) intake is recreational.

Usable marijuana does not present a problem. All usable marijuana is sold in carboxylated form, and its behavior—potent when heated, inactive when unheated—is generally well understood by consumers. For usable marijuana and concentrates (i.e. products likely to be subjected to heat), potency can be calculated by including THC-A and CBD-A under categories 'Total THC' and 'Total CBD.' (Section III discusses complications with these methods.)

Prepared edibles/beverages, however, are *not intended to be heated* after sale and pose the risk of problematic changes in potency. There are two obvious risks: (A) that producers intentionally 'spike' these products with THC-A and encourage consumers to heat the product to activate it, in order to exceed THC dosage limits, and (B) that dosage is accidentally changed over time, as THC-A gradually transforms into THC. Regulations can prevent this by requiring a 'cap' on the allowable percentage of decarboxylated cannabinoids in prepared edibles/beverages. With such a cap in place, potency labels for these products need not include THC-A and CBD-A in their potency score.

Limiting deterioration.

Over time, THC will break down into CBN, and the chemical content of cannabis will change in more complex ways. This represents a challenge for accurate potency labeling. Product deterioration can be limited by ensuring proper packaging and storage, and by shortening the time between potency testing and sale to the consumer.

Regulating claims of off-label cannabinoids and medical effects.

Consumers seeking particular medical or psychoactive effects, whether valid or unsubstantiated, may specifically seek products rich in THCA, CBDA, CBC, CBG, or other cannabinoids. These chemical contents might be marketed in such a way that avoids medical claims, which are prohibited by regulations, for instance with labels touting "high-CBG." Regulators have several options for dealing with this type of claims. They may be disallowed completely, allowed only when verified, or allowed without any regulation. A reasonable "middle ground" approach would be to prohibit unverified claims of chemical content. Under that policy, products would be able to market levels of any cannabinoid, so long as the claim is supported by credible testing results (using certified standards, where available). This is in keeping with the general principles of consumer protections, which

disallow fallacious claims. If products are allowed to make non-medical statements about the "health-supportive" effects of cannabinoids they contain, like those made by herbal supplements in health food stores, they might be required to comply to the same standards: providing potency testing, as well as reference to at least one peer-reviewed study showing statistically significant positive medical/subjective effects.

Preventing label "crowding."

Labels should be designed in a way that considers the limits of the consumer's attention span and pharmacological knowledge. Simpler labels are easier for (especially low-information) consumers to understand, and effectively direct the consumer's focus in predictable ways. On the other hand, a label crowded with more statistics is more vulnerable to misinterpretation or negligence by the consumer. Accordingly, chemicals not known to have significant therapeutic or psychoactive effects should not be required to appear on potency labels. Alternative policies for addressing this same problem are to include graphical representations of chemical contents or supplemental educational materials. Marijuana's complex pharmacology complicates the design for graphical displays. Feasible options might classify product potency along a single-dimension (perhaps grouping product into color-coded low, medium, and high potencies) or they might display both product potency and quality (perhaps with a two-dimensional chart graphing total THC against CBD:THC ratio).

Terpene "fingerprinting."

Terpenes appear to influence the psychoactivity of cannabis, and may account for the differences in subjective experience that consumers attribute to different strains. The specific effects of individual terpenes are poorly understood, and are not significant enough to warrant mandatory labeling. Nonetheless, there may be the possibility of terpene profiling being used to verify the cultivar—and therefore the experience—that the consumer is purchasing. Rules to reduce misinformation to the consumer are discussed in Section 3.

Proceeding in the absence of chemical standards.

Since marijuana testing is still in its early stages of development, many procedures are unstandardized. In the absence of standards, laboratories perform proprietary processes; accordingly, their results may not be accurate or consistent across different laboratories. There are two ways to think about such in-house standards: as better-than-nothing or best-available alternatives to certified standards, or as unreliable and therefore potentially misleading or unsafe. Given none of the minor cannabinoids are known to be psychoactively important, or to pose public health risks, low accuracy in this setting may pose little concern.

II. Bioavailability and Implications for Testing Accuracy

The effect of cannabis depends on both the product's chemical content, the user's method of intake, and users level of experience or naiveté. The bioavailability of cannabinoids varies based on the mode of ingestion: whether they are eaten, smoked, vaporized, and so on. Different intake methods lead to different metabolic pathways and experiences for the consumer, including:

- The fraction delivered to the body (e.g. that fraction that is neither destroyed nor released into the environment, perhaps via smoke).
- The metabolic mode and efficiency (e.g. first-pass metabolism in the liver).
- The rate and peak of cannabinoid accumulation in the bloodstream.

These are important considerations for potency testing policy. If there is significant uncertainty about how much cannabinoid content will be made bioavailable, and about the quality and intensity of the resulting subjective experience, very precise potency labels become less useful. If, for example, one user consumes cannabinoids via dabbing and another consumes via a hybrid tobacco-marijuana joint, the differences in potential bioavailability inherent to these very different methods of intake dwarf the uncertainty caused by a ±1% or a ±10% degree of potency label inaccuracy..

Note that CBD and THC have shown similar pharmacokinetic profiles (Huestis, 2007), and therefore are similarly affected by each of the following intake methods. These cannabinoids are not distinguished from one another in this section.

Smoking

The bioavailability of smoked THC is highly variable, ranging from 2% to 56% (Huestis, 2007), and is commonly reported to average around 15-20%. Heavy users appear to be more efficient, inhaling an average of 25%, compared to roughly 12% for occasional users. This picture is complicated by many other factors: even with a standardized, computer-paced procedure specifying the number of puffs and the inhalation and breath-holding time, variability in blood concentrations of cannabinoids can vary by as much as four times (Grotenhermen, 2003).

Vaporization

Compared to smoking, vaporization is thought to deliver cannabinoids at higher rates and with less variability. For vaporized cannabis, bioavailability rates vary based on several factors, including vaporization temperature and social setting. A study of the high-end "Volcano" brand vaporizer finds that it extracts between 36-61% of cannabinoids in the sample material (Gieringer, 2004). Another study, comparing bioavailability between smoking and vaporization, found that vaporization resulted in slightly higher blood cannabinoid levels at both 30 minutes and one hour after inhalation. However, substantiated claims for different bioavailability patterns in vaporization are both too few and too modest to support any particular policy decision (Abrams, 2007).

Dabbing

Dabbing is a method of vaporizing cannabis extract. A very small amount of concentrated extract can be vaporized and inhaled in a quick, efficient manner. This method exposes the consumer to a much higher number of mg THC in a single inhalation than any other method currently used. While the metabolic efficiency is probably similar to smoking or vaporization, the process itself exposes the consumer to much more THC at a faster rate.

Oral ingestion

THC bioavailability upon oral ingestion is less variable than smoking, with estimates ranging from 4% to 20%. A reputable assessment estimated 6% bioavailability from a chocolate cookie (Huestis, 2007), while another paper found 7% bioavailability from 10 mg dronabinol (Grotenhermen, 2003). One factor that makes oral ingestion less variable is that no material is lost to the outside environment. While some smoke or vaporized material never even makes it into the user's lungs, the oral route of ingestion ensures that the entire chemical dose enters the user's system.

Compared to other ingestion routes, oral ingestion produces distinctively high levels of 11-Hydroxy Δ9 THC (or 11-OH Δ9 THC) within the liver. Once absorbed, THC is oxidized by the cytochrome P450 hepatic mixed-function oxidase system into 11-OH Δ9 THC, and further metabolized to inactive 11-nor-9-carboxy-THC (THC-COOH). This metabolic process can delay the onset of psychoactivity for 30-90 minutes., and causes 11-OH Δ9 THC levels to surpass THC levels, peaking higher and persisting longer. It may take as long as two hours for THC levels to increase from zero, and more than ten hours to return to zero. 11-OH Δ9 THC persists for markedly longer, with levels still at their peak some 14 hours after initial consumption (Huestis, 2007).

Oromucosal absorption

Cannabinoids can also be absorbed within the oral cavity. Sativex, for example, is intended for sublingual absorption, partly to avoid first-pass hepatic metabolism, whereby much of a drug's active agents are absorbed by the liver and gut rather than passing through to the circulatory system (Huestis, 2007). Both pure THC and Sativex have similar sub-lingual administration bioavailability profiles, with absorption rates reported around 11-13% (Karschner, 2010). (That study may over-estimate efficiency and consistency, since doses were delivered directly to patients' buccal mucosa by trained physicians.) Even in such studies, there is significant variability in bloodstream levels of THC between individuals (Karchner, 2010).

Thus oromucosal absorption is perhaps the most consistent route of administration in clinical settings, but it is unclear how this can be generalized to actual use by consumers. Actual application of lollipops or lozenges to the buccal mucosa (the inner lining of the cheeks), versus product swallowing, is likely to be highly variable, and the properties of

texturing and flavoring products (e.g. other fat, sugar and chemical components) contained in the product may also impact absorption rates.

Topical absorption

Cannabinoids are highly lipophilic, allowing them to cross into the bloodstream when applied to the skin. Topical products, commonly packaged as skin creams or lip balms, capitalized on this property. Transdermal application has the advantage of bypassing first-pass metabolism, and is thought to deliver THC at a slow pace (Huestis, 2007). There is little data available on variability, but it can be assumed that consumers will neither use carefully measured doses, nor apply to a standardized area or at a standardized product thickness. However, topical products are usually dosed quite low and as a result are not very psychoactive.

Section II Conclusion: Implications for testing

The high variability in bioavailability of cannabinoids, both within and across different methods of intake, limits the usefulness of precision in potency labels. This variability introduces an uncertainty about psychoactive effect that cannot be eliminated, even if cannabinoid content is tested for with very precise methods, with small lot sizes, and conveyed to the consumer with effective product labels. An overwhelmingly large share of the variability in psychoactive effect arises from the method of use and drug metabolism, rather than the chemical contents of the product.

However, most of the studies presented above discuss only *inter*-person variability, not *intra*-person variability, For instance, two people may have very different absorption efficiencies in smoking a joint, based on their inhalation habits, or in eating a brownie, based on their metabolisms and fullness of their stomachs. However, to the extent that those individual factors are consistent across that person's lifetime, intra-person variability may be substantially lower. If intra-person variability is low, that would strengthen the argument for higher-precision testing, since a single individual could learn over time how they respond to, say, a 20 mg THC product as opposed to a 16 mg product. Nevertheless, a single individual may still eat meals at different times before eating a cannabis-infused product, or smoke, roll, and share a joint differently in different situations.

It is difficult to quantify the uncertainty introduced by different methods of intake. Even if method of intake is held constant, many of the studies presented above suggest intake variability greater than +/- 100%, and sometimes much greater. This data suggests that potency labels need not seek greater precision than, for instance, a 95% confidence interval of ±15%, which incidentally is the tolerance allowed for cannabis produced by Bedrocann for the Dutch Government (Gieringer, 2011).

III. Testing and Labeling Practices

This section examines issues associated with the testing and labeling of cannabinoid levels. In the WA medical market today, stores, growers, infused-product makers, and co-ops are under no obligation to report any testing results on plant material or edibles they sell. Even the most model retail outlets do not insist on 'tested only' material from their wholesalers. A low level of consumer demand for testing means that some testing does occur, but these testing practices are minimally regulated and often unreliable. A grower or infused-product maker will often have one batch or crop of their product tested and use those results as representative in the future.

A. Testing methodologies and complications

Testing methodology: HPLC, GC-FID, GC-MS, and TLC

Cannabinoid analysis methods include Thin Layer Chromatography (TLC), Gas Chromatography, often coupled with Flame-Ionization Detection (GC-FID) and/or Mass Spectrometry (GC-MS), and High Performance Liquid Chromatography (HPLC). Of these, only gas and liquid chromatography should be used for quantification; thin layer chromatography is suited only for identification (however, some labs violate this principle).

The principal difference between liquid and gas methods is their treatment of cannabinoids in their acid forms, i.e. THCA and CBDA. While HPLC methods can directly quantify both THC and THC-A, the GC-FID can only quantify THC. The GC-FID moves the sample through a high temperature injector designed to vaporize the sample for analysis, however the heat in the injector causes the unintended action of decarboxylating the acidic cannabinoids prior to detection; in the process, some of the acid components will break down into other chemicals, remaining undetected. The total of detected cannabinoids is usually reported as 'Total THC' and 'Total CBD.'

Because HPLC methods count the entirety of the acid component, but GC methods count only the portion that decarboxylates into THC, HPLC analysis does not usually agree with GC analysis of the same extract (deCesare, 2011). If THCA levels are high relative to THC (as is commonly the case in fresh plant material), the difference in THC levels can be as high as 27%. There are methods for overcoming this weakness of the GC method, including performing an initial reaction (e.g. derivatization of carboxylic acids) on THCA and CBDA compounds to make them stable and identifiable via GC-MS.

This drawback inhibits most GC methods from identifying incomplete decarboxylation in products not intended for post-sale heating, such as baked edibles, beverages, sub-lingual sprays, and topical creams. If these kinds of products are incompletely decarboxylated, the dosage they contain may be unstable over time: as they sit on retail shelves awaiting sale, their constituent THC-A and CBD-A will slowly decarboxylate into THC and CBD, thereby increasing total potency. HPLC methods have the advantage of being able to detect any remaining, carboxylated acid components. If a cap is placed on THC-A content in edibles and beverages, HPLC will allow producers to identify incompletely decarboxylated products and comply with regulations. If no such cap is in

place, an alternative is to require labeling of THC-A in order to warn consumers. Popular GC methods would not be able to notify the consumer in this way.

Difficulties in analyzing edibles

Most cannabis testing labs do not test 'finished good' edibles. The complication of adding sugar, flour, colors, fats, or chocolate to a sample for analysis makes for a considerable amount of method development. A lab must determine if all the cannabinoids have been extracted from these complicated matrices, and the dissolved sample must also be 'cleaned' of interfering compounds before an accurate analysis can be performed. This is a complex endeavor, which must be developed for every new infused product submitted for analysis. Only two of the laboratories surveyed by BOTEC (Haneman, 2013) said they have tested any finished goods.

Instead, edibles have typically been assessed indirectly: labs test the potency of cannabis extracts, and then infused product makers calculate how much of the extract to use to achieve the desired dose. In the new I-502 market, it may be appropriate to test edible products directly. This represents a relatively new and cost-intensive development for some labs.

Testing for minor cannabinoids

Chemical standards to test for minor cannabinoids are not readily legally available to the cannabis testing labs; however, standards may be available in Europe or in the US with a DEA Registration Certificate. This is of particular concern with CBDA, for which no reputable standard exists. Nonetheless, CBDA standards appear to be available on the gray market, since some labs offer testing for CBDA. Until standards for these chemicals are developed, it would be problematic to require testing for that substance.

Testing for terpenes

Plants can easily be fingerprinted as being of either *C. Sativa* or *C. Indica* types (although it is now widely accepted that these are different cultivars within a single species) (Hillig, 2004), but a 2012 study was able to distinguish the terpene profiles of two popular cannabis varieties, "White Widow" and "Amnesia" (Hazekamp, 2012). As cultivar-verification techniques are refined, it may become common for consumers to seek products that have been shown to be genuine through laboratory testing.

In anticipation of such testing, the Board may consider rules that protect consumers from misinformation. However, given terpene profiling is in its infancy, it is not possible to narrowly specify appropriate methodologies. Moreover, even with quality testing, it will be difficult to protect consumers from false claims about the strain used in a product: terpene profiles are not yet well-established, may vary considerably, and will likely be contentious. There is therefore no neutral standard by which to assess whether a specific terpene profile does or does not match the claimed strain. For the present, a market-based solution will be sufficient: terpene profile results, and the methodologies by which they were

acquired, should be made available to consumers on request wherever laboratory verification of a strain is claimed. Consumers can decide on this basis whether they are satisfied and wish to continue purchasing the product.

Typical test accuracy

In 2010/2011, Project CBD and California NORML conducted an investigation of laboratory testing accuracy. Results were concerning: for one identical sample tested across 10 labs, and four separate times at each lab, the reported THC ranged from 4% to 14%. After excluding the 10 least accurate assessments, the range was 8.4% to 12.5%, or around ±20% from the mean (Gieringer, 2011). One lab failed to adjust for the higher molecular weight of THCA in deriving a 'Total % THC' value, thereby over-reporting THC content. Reported CBD in one lab was off by more than a factor of five, and reported CBN for one sample ranged from 0% to 1.44%. Finally, labs using GC methods generally found higher results than those using HPLC, and sometimes much higher (an average of 40% higher for some samples). There is no clear explanation for this discrepancy.

To accentuate the concern presented by these results, the authors of the study noted that the participating labs gave these samples extra attention, often re-testing them and correcting misreported potencies of their own volition. These labs may not be so careful when they are not actively being surveyed. The study is now two years out of date, and in this rapidly moving industry the situation appears to have improved markedly. Recent data from the Association of California Cannabis Laboratories (ACCL, 2012) suggests that test results generally fell within +10% and -20% of actual cannabinoid values. The issue of ensuring laboratory competence and proper methodology can be addressed with proper laboratory accreditations and/or standards, and is discussed in a companion paper (Anderson, 2013).

Testing error tolerances

Testing tolerances or margins of error should be specified as 95% confidence intervals and in % terms, e.g. ±15%, rather than absolute terms e.g. ±1 mg. This would mean that, for example, if laboratories were to analyze a cannabis product that contained 10mg of THC 100 times, on average 95 of the test results would find a concentration that was within ±15% of the true concentration (i.e. 8.5mg to 11.5mg).

Absolute error margins should be avoided, given they allow large uncertainty for low-concentration products but place stringent requirements on high-concentration products. For instance, a ±1 mg tolerance represents 50% error on a 2mg product but 7% error on a 15 mg product.

Still, percentage-based tolerances may need to be relaxed at very low detection levels, perhaps below 1%, given high-resolution analysis becomes more difficult. Finally, tolerances could perhaps be more lenient (e.g. ±25%) on non-psychoactive compounds like CBD, given the lower risks associated with dosage error.

B. Labeling practices

Calculating 'Total %THC' or 'Total mg THC'

When HPLC (or other methods) resolve THC and THCA separately, they are typically combined to derive a figure for 'Total mg THC' or "% Total THC." However, this calculation is not as simple as adding %THC by weight and %THC-A by weight and arriving at "Total THC%." Instead, the calculation should account for the different molecular weights of THC and THCA. The molecular weight of THC is 314.45, only 87.7% of the weight of its carboxylated acid form, THC-A. This means that if 10 mg of THCA were to be fully decarboxylated, it would turn into 8.8 mg of THC; although the number of molecules would stay the same, each molecule would be lighter. Therefore, any calculation intended to describe the sum of carboxylated and decarboxylated THC content should apply a 0.877 multiplier to the concentration of THC-A. This results in the following formula:

*(%THCA*0.877)+ %THC = % total potential THC.*

Some laboratories modify this formula in order to provide higher potency scores, for instance by adding % CBN and % Δ8-THC on the left-hand side of the equation. Because CBN and Δ8-THC have somewhat different and markedly less potent psychoactive effects than THC, they are generally considered inappropriate for inclusion in a "total THC" metric.

Potency labeling for useable marijuana

The potency of useable marijuana is sometimes reported as a percentage of "dry weight" and sometimes reported as a percentage of weight "as is." For a cannabis flower within that range of moisture content, the "dry weight" method generates potency scores 10-16% higher than the "as is" method. This might explain why the "dry weight" method is more popular, since it generates higher potency ratings by subtracting weight from the denominator; but neither method is correct or incorrect. Regardless, a standard is required to provide consistency across different testing laboratories. Since the dry weight calculation is more commonly used by laboratories, a sensible regulatory approach would be to require all laboratories to calculate chemical concentrations as a percentage of "dry weight."

Potency labeling for edibles, beverages, e-cigarettes, tinctures, and topicals

For these products, potency is sometimes reported as total milligrams per serving; other times, potency is either not reported at all or reported according to an unquantifiable scale, e.g., 1X, 2X, 3X, 4X. In the latter case, 'X' is sometimes compared to a serving, but it in no way represents a precise or consistent dose in milligrams.

Incomplete decarboxylation is another issue unique to marijuana-infused products. As discussed earlier, incompletely decarboxylated products can be identified by measurable amounts of THC-A or CBD-A. Compared to if they were completely decarboxylated, these products are unstable as cannabinoids slowly decarboxylate over time. For instance, an incompletely decarboxylated edible containing 10mg THC and 10mg THC-A could eventually degrade into a 17mg THC serving.

Incomplete decarboxylation is also an indicator of sloppy procedures. Infused product makers typically do not knowingly "waste" cannabinoid content by delivering them in inactive forms; when they do, it is by accident. An infused product maker who fails to completely decarboxylate an extract or infusion should be suspect for other errors, which might result in inaccurate dosage, short shelf life, or risks to consumer health. In a worst case scenario, an edible could be purposely 'spiked' with THCA so the consumer could bake or otherwise heat the edible so that the THCA converts to THC, raising the psychoactive content in excess of the maximum allowable per-serving or per-package content allowed for marijuana-infused product.

In light of these complications, incomplete decarboxylation should be either prohibited, limited, or identified on the potency label. This is not a clear choice. A full prohibition would disallow the sale of products high in THC-A or CBD-A, which may be sought for alleged medical benefits. On the other hand, identifying THC-A and CBD-A on the potency label might fail to inform a consumer who has not yet learned their significance, and the effort also may add to the costs of testing and reporting.

Section III Conclusion: Implications for testing

In terms of different testing procedures:

- GC-FID is sufficiently accurate for material to be heated, i.e. fresh plant material, or concentrates. GC is also adequate for edibles made from an analyzed, pre-approved, adequately decarboxylated extract.
- HPLC and more advanced GC methods capable of detecting acidic cannabinoids are excellent for all detection purposes, and necessary for detecting THCA (for example, to prove complete decarboxylation into THC for edibles, beverages and extracts).
- TLC should be disallowed due to its low quantitative accuracy

Test results should be expressed on final labels in terms of mg of cannabinoid present per relevant unit (portion, milliliter, gram, etc.).

Error tolerances should be expressed as 95% confidence intervals in ±X% terms. ±15% is a reasonable level with precedent in the Netherlands, is useful for consumers, and is within the reach of quality laboratories. More relaxed tolerances may be appropriate when quantities are sub-1% of dry weight, and for non-psychoactives like CBD. Achievement of these standards should be verified periodically by a third party auditor using multiple analysis methods.

Prepared edibles, beverages, and other marijuana-infused products are cost-intensive to test directly, as a finished product. An already popular and more cost-effective option is to test only the cannabinoid extract, after it has been fully decarboxylated but before it is infused into the product. That strategy might be complemented by occasional random tests on the finished marijuana-infused product. A periodic spot testing of finished products could be a good method of checking dosage accuracy, and/or an inspection of dosing procedures by LCB. Infused edible production logbooks should demonstrate dosing amounts and clearly document dosage calculations on a per batch basis.

Incompletely decarboxylated marijuana-infused products represent a risk for accidental overdose, since the active THC content of these products can actually increase over time. One viable policy response is to require complete decarboxylation of all marijuana-infused products; on the other hand, this option would preclude markets for high THCA or high CBDA products, which may be pursued for medicinal purposes. (This concern is lessened if the commercial market is not expect to provide for medicinal purposes, which may be met through the medical market.) A second option to reduce this threat is to inform the consumer about both the risk of incomplete decarboxylation and the levels of carboxylated THC and CBD in a particular marijuana-infused product package.

If included on the potency label, 'Total THC' should be calculated in a consistent and accurate manner.

- Where HPLC methods are used, 'Total THC' should adjust for the differences in molecular weight of THCA and THC.
- Moisture content should be recorded, and potency results reported per dry weight.
- Neither CBN nor Δ8-THC should be included within 'Total THC'.

Finally, terpene content may be significant for the psychoactive and health impacts of cannabis, and evidence suggests that terpenes can be used to distinguish between cannabis strains. Terpene profiling techniques are still developing, but may soon allow consumers to seek verification that strains are genuine. Rules about technical standards are unnecessary at the present time, and should instead depend upon transparency to provide the incentive for quality. Consumers should be provided with information on the analysis methodology, as well as the complete terpene analysis results, on request.

IV. The Costs of Cannabinoid Analysis

This section explores the costs associated with testing methods.

A. Prices as reported by laboratories

Laboratories tend to offer three basic grades of testing: basic potency profiling, advanced potency profiling, and a full suite combining potency, terpene detection, and pesticide, microbial, and fungal testing. Compared to basic potency profiling, the advanced package detects a wider array of minor cannabinoids and a range of terpenes. Tests perform via liquid chromatography rather than gas chromatography have the advantage of detecting THC-A and CBD-A.

Based on a review of the testing market at present, the price ranges for different services are as follows:

- $30-50 for basic GC profiling of THC and CBD, sufficient for potency tests on products that will be heated (e.g. raw flowers) or that are known to have already been full decarboxylated (e.g. any product produced from a fully decarboxylated extract).
- $60 for more advanced profiling, typically a HPLC test that additionally reports on THC-A and CBD-A. This is necessary for products that need to prove THC-A or CBD-A presence (e.g. health-supportive products claiming THC-A content) or absence (e.g. to prove complete decarboxylation for products to be consumed cold).
- $100-120 for full potency, pesticide and microbial assessment.

It is difficult to predict whether prices will rise or fall going forward. On the one hand, I-502 will impose increased regulatory costs that may increase the cost per test. On the other, costs per tests might drop as testing volumes increase (thanks to testing requirements in I-502) and as the industry matures. Regardless, as discussed in Section B, costs are likely to remain minor relative to cannabis product value.

B. Anticipated total cost burden

The cost burden of testing depends upon the lot size. The following table displays the costs per gram for a full $120 test (potency, pesticide and microbial) for different lot sizes. (For this table, cannabis is assumed to sell for $12/gram, a rough estimate of current Washington medical marijuana market prices.)

Lot size	Lot size (g)	Cost per test	Cost of testing per gram	Cannabis price per gram	Test as % of retail value
One ounce	28	$120	$4.29	$12	35.7%

6 ounces	170	$120	$0.71	$12	5.9%
One pound	454	$120	$0.26	$12	2.2%
2 pounds	907	$120	$0.13	$12	1.1%
3 pounds	1361	$120	$0.09	$12	0.7%
5 pounds	2268	$120	$0.05	$12	0.4%

As shown above, the direct cost of testing at very small lot sizes is onerous, but much less burdensome at a lot size of five pounds.

Testing introduces other types of costs, besides the price paid for testing services. Some batches might fail threshold tests for contaminants, for instance if pesticides or dangerous molds are detected at unsafe levels. Similarly, if a potency test discovers that a producer's crop is substantially lower in cannabinoid content than expected, its value may be substantially reduced. Figures on potency failure are not available. (For pesticide, microbial, and fungal testing, failure rates of 1-5% are commonly reported in markets with voluntary testing.) For both potency and contaminant tests, there are ancillary costs; for example, the work of dividing the cannabis into lots and of shipping product to and from the testing service. Similar to the costs displayed in the table above, these ancillary costs can be reduced by allowing larger lot sizes.

Section IV Conclusion: Implications for testing

Anticipated costs of testing are in the range of $50-60 for potency testing, and $100-120 for full potency, pesticide and microbial testing. There are not significant differences in cost between GC and HPLC testing; the choice of testing methodology may depend more on the specific testing needs than price conerns.

At a required lot size of five pounds, the direct costs of potency and contaminant testing represent approximately 0.4% of the product's retail value. However, the costs of testing appear more expensive if viewed as a percentage of the costs of production or to the revenue of any given firm within the supply chain.

V. Conclusion

Potency label design

Both cannabis' chemical contents and the ways in which people intake and metabolize these contents are complex. Labels, however, should aspire to be simple. The consumer may benefit most from a label that directs attention to where it is most needed, rather than offering a wider range of data that is overwhelming or demands pharmacological understanding. At best, the data that the consumer cannot understand will be ignored; at worst, they will be misinterpreted. Accordingly, cannabinoids with unproven therapeutic and psychoactive effects do not warrant inclusion on the potency label.

It may be sufficient to require only "Total THC" and "Total CBD" on product labels. THC is the primary psychoactive agent in cannabis. Although CBD is not psychoactive in isolation, it has been shown to significantly moderate the effects of THC when taken in combination. There are arguments for including other cannabinoids. THC-A and CBD-A would indicate incompletely decarboxylated – and therefore unstable – marijuana-infused products. As a breakdown product of THC, CBN can indicate product freshness. However, these same goals could be achieved by other methods to prevent incomplete decarboxylation and by time-stamping potency labels with a date of expiry. (Steep Hill Lab, for instance, uses a 2-month expiration date.) There are also arguments for reporting terpenes and other noncannabinoids thought to affect the user experience. However, at least based on the science currently available, including other cannabinoids and non-cannabinoids carries little benefit to the consumer: none of them are known to both have particularly strong effects or to appear in commercial cannabis in meaningful quantities. Label claims for these cannabinoids might be left to industry discretion but enforced by regulation. For instance, perhaps if a producer advertises CBG, CBC, and other cannabinoids on a product, it should be reported in smaller print than the required cannabinoids, and its claims verified by regulating agencies.

An idea for future contemplation is to design labels and associated pamphlets to encourage consumer awareness of CBD content. The current peer-reviewed literature suggests that encouraging consumers to switch from high-THC product to higher-CBD product might mitigate some of the public health costs of cannabis, perhaps resulting in fewer emergency room visits for panic attacks and lower rates of dependence. Products could, for example, be marked with additional labels when they meet a specific THC:CBD ratio standard or CBD level, such as:

- *"CBD balanced"* for products exceeding CBD:THC ratios of 1 : 5. Claims such as "may reduce anxiety associated with THC" for such products might be allowed on packaging or in pamphlets sold with transactions.
- *"High CBD"* for products exceeding CBD:THC ratios of 1 : 2, or perhaps exceeding 4% CBD content.

Ensuring proper calculation of "Total THC"

Potency results should be reported on a dry weight basis. If reported, 'Total THC' should adjust for the differences in molecular weight between THC and THC-A, and should not

include fundamentally different chemicals such as CBN or Δ8-THC. For testing methods that quantify THC-A and THC separately, this is encapsulated by the following formula:

(%THCA.877)+ %THC = % total potential THC.*

The same principles apply to CBD, considering its carboxylated (CBD-A) and decarboxylated (CBD) forms. An analogous formula, with the same multiplier for molecular weight, applies for CBD.

For marijuana-infused products, cannabinoids should be either fully decarboxylated before sale or clearly labeled as incompletely decarboxylated. These products are unstable and can become increasingly potent while they sit on retail shelves, as non-psychoactive THC-A slowly decarboxylates into THC. This exacerbates the risk for accidental overdose, which is already inherent to marijuana-infused products. Requiring complete decarboxylation for all marijuana-infused products, or mandating a limit on the amount of allowable THCA, would be the strongest action to reduce this risk of dose instability, at the cost of eliminating the market for products intended to deliver THC-A and CBD-A for alleged therapeutic benefits.

Label claims of minor cannabinoid content and health effects

Some firms will likely make marketing claims about content of other cannabinoids (such as "high CBV", "high CBC", "high THC-V", and so on). This raises several questions.

Should such claims be allowed on product labels? On one hand, producers should be unconstrained from communicating their product's content; on the other hand, these claims may mislead the consumer into inferring proven psychoactive or therapeutic effect or distract the consumer from more pertinent chemical contents.

If these claims are allowed, what is the appropriate burden of proof? It appears simple to require that any advertised cannabinoid(s) are backed up by quantified testing results. However, in many cases, particularly for many minor cannabinoids, certified testing standards are either unavailable or difficult to acquire by I-502 firms. In such cases, there appear to be two options:

- Require testing using certified standards. This would protect the integrity of label claims, at the cost of limiting their scope. It would effectively disallow claims of minor-cannabinoid content, such as CBD-A, for which standards have not yet been developed.
- Allow the use of non-certified and in-house standards, but *only until a certified standard becomes available*. This flexible approach allows for a wider range of label claims, but sets a lower bar for potency testing. (Since these minor cannabinoids appear to be relatively non-psychoactive and benign, this may be an acceptable cost.) Testing labs should post a confirmed certificate of analysis on their website for every lot of off-label standard they make and use.

Going one step further, should products advertise health-supportive effects? One option is to treat such products as in the same way as non-medical, minimally-regulated herbal supplements. Producers of herbal supplements can legally make non-medical claims about

the 'health supportive' properties of products, so long as they quantify the level of the active compound and cite a peer-reviewed journal demonstrating statistically significant evidence of the claimed effect (United States code, 2010).

Terpene 'fingerprinting' to verify strains

Rules should specify that claims about strain verification through chemical profiling be made transparently, with the methodology employed and the results available to consumers on request. In coming years, further scientific research will clarify the feasibility of terpene fingerprinting and implications for regulators.

Testing methodology and costs

Testing should be conducted by GC, HPLC, or better, with older approaches such as TLC disallowed for quantification. GC-FID is sufficiently accurate for material expected to be heated, i.e. fresh plant material. HPLC and more advanced GC methods capable of detecting THCA are excellent for all detection purposes, and necessary for detecting THCA (for example, to prove complete decarboxylation into THC for edibles, beverages and extracts).

Anticipated costs of testing are in the range of $30-60 for potency testing, and $100-120 for full potency, pesticide and microbial testing. The cost burden depends upon the lot size and the list of pesticides tested for, with costs falling to 1% or less of total product value where lots are two pounds upward. These costs are likely to increase as potency testing becomes regulated. Regardless, costs do not appear to present any risk for financial viability at lot sizes 2 pounds and above.

Costs for testing finished marijuana-infused products are more complex. It may be more effective to require regular testing only of the cannabis extract ingredient, after decarboxylation but before infusion. This may be complemented by occasional tests of finished marijuana-infused products on a random basis to ensure accurate dosage methods.

Limits on precision: biological heterogeneity, intake methods, and absorption rates

As discussed in Section II, popular methods of cannabis intake are extremely inconsistent ways to intake cannabinoids, both in terms of inter-person and intra-person variability. Smoking cannabis from a joint, pipe, or bong, vaporizing it, and taking it orally or oromucosally all deliver psychoactive material to the body at different overall efficiencies and speeds. This changes the total volume of cannabinoids metabolized by the user and that pattern over time, including the timing, height, and duration of the peak of the high. These variables are compounded by the different physiologies and intake techniques of different users. This is particularly true with usable marijuana, but still important for marijuana-infused products. The oral routes of administration are highly variable, even if less so than smoking and vaporizing.

This represents a serious source of uncertainty in translating the cannabinoid contents of a package to the quality and intensity of subjective experience for the user. It places a pragmatic limit on the value of high degrees of precision in cannabis testing and labeling.

Error tolerances of ±15%, as a 95% confidence interval, in reported cannabinoid levels may be appropriate, and has precedent in the Netherlands. Such a tolerance interval is made more acceptable considering the varying efficacies of different intake methods and the wide range between a suggested dosage unit of marijuana and a dose likely to cause acute overdose. These tolerances may be harmlessly relaxed when detecting quantities less than one milligram and for non-psychoactive cannabinoids. Tolerances can be verified periodically by a third party auditor using multiple analytical methods, or by a number of other schemes (Anderson, 2013).

Consumer education should emphasize the unpredictability of a given individual's response to a cannabis product, especially between products with different delivery mechanisms. Consumers should be advised to use extra caution when using unfamiliar products. In particular, they should be made aware of the complications inherent to edible products, including the multi-hour delay before initial psychoactivity, its long intoxication time, and its variability based on whether taken on an empty or full stomach.

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