Cannabis Testing for Public Safety – Best Practices for Vermont Analytical Laboratories

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Summary Recommendations for Regulators

1. Testing for public safety. *Cannabis* and *Cannabis*-derived products intended for human consumption, including marijuana, hemp and their extracts, must be *sampled*, *tested*, and *labeled* prior to retail sale.
(a) *Sampling.* A licensed laboratory or third-party body must certify that the samples are representative of the lot or batch and were obtained according to standardized procedures.
(b) *Testing.* Laboratory testing must include measurement of potency and levels of contaminants by a laboratory operation accredited according to criteria for competence set by the International Organization for Standardization (ISO) 17025. All lots must be tested for potency; acceptance sampling of at least 10% of lots must be tested for contaminants.
(c) *Labels.* Consumer labels must at minimum list the potency of the primary active ingredients, delta-9 tetrahydracannabinoid (THC) and cannabidiol (CBD), as 95% confidence interval around the measured point estimate; they must also provide warning of the risk of exposure to children.

2. Laboratory Regulation. Laboratories must follow licensing, accreditation, and management protocols established by the State of Vermont.
(a) Laboratory operations that perform testing of *Cannabis* for public safety must be licensed by the State and accredited to the ISO 17025 standard; the assessment and accreditation process must be carried out by an International Laboratory Accreditation Cooperation (ILAC) third-party body that is itself accredited to the ISO 17011 standard.
(b) Laboratory operations must be housed in secure facilities fulfilling the same security requirements defined by the State for retail, production, and cultivation.
(c) Laboratories must be supervised by a qualified scientist with a PhD or equivalent industry experience (i.e., 3 or more years), in quantitative testing of *Cannabis*, agricultural, food, or pharmaceutical products.
(d) Laboratory operations may be associated with cultivators, producers, wholesalers, retail stores or medical dispensaries as long as they are licensed by the State and accredited to the ISO 17025 standard by an International Laboratory Accreditation Cooperation (ILAC) third-party body.

3. Financial considerations. We posit that individuals will be willing to pay a premium for certified consumer-safe products, and that this premium will be equal or greater than the costs associated with quality control. To explore this hypothesis, we produced a financial model that calculates the total costs for a commercial cultivator or producer of *Cannabis*-based products to perform our recommended safety testing (Appendix 1). This model shows that - given the stated assumptions - the costs of testing for potency and quality range from less than 1% (i.e., 0.87%) of the total value of the product when the product is priced at $18/gram to 2.53% of the total value of the product when the product is priced at $5/gram. The recommended testing strategy would therefore add very little in cost to the producer.

4. Regulatory guidance. As the industry matures and scientific data accumulates, regulatory guidelines should be revised. The State should establish a *Cannabis* Scientific Advisory Council to set thresholds for contaminants, make decisions on product recalls, and oversee the allocation of State funds for *Cannabis* research from sales tax revenues. Specifically, the Council should provide policy guidance in the creation and implementation of a *Cannabis* Science Research Grant Program to the Vermont State Colleges and Universities for scientific research on the basic science and clinical effects of *Cannabis* and its derivatives.

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I. Introduction

This paper provides a summary of the best practices for analytical laboratories that perform testing of *Cannabis* and *Cannabis*-derived products intended for human consumption. Specifically, we address the following questions for regulators and policy makers interested in ensuring safety as the Vermont *Cannabis* industry evolves: *How should Cannabis products be tested for public safety? How should the testing laboratories be regulated and accredited? What will it cost to do the recommended testing?*

In the absence of guidance from the United States Department of Agriculture (USDA), the Food and Drug Administration (FDA), or the Environmental Protection Agency (EPA), regulatory agencies in states allowing retail sales of *Cannabis* and *Cannabis*-derived products must decide whether safety testing will be required of these products. States also must decide how to inspect and certify the laboratories that will perform the necessary analytical testing. We provide specific recommendations that can serve as a roadmap for policy makers seeking direction in the uncharted territory of *Cannabis* in public health and safety considerations. This information should be widely generalizable to governmental regulatory bodies and private sector interests throughout the United States who are confronted with similar challenges as those faced in Vermont.

Analytical testing of commercially available *Cannabis* for safety and potency is increasingly recognized as a critical and necessary component of the industry, for several reasons:

- Public health concerns mandate safety testing of commercial products intended for human use and consumption. Laboratory testing of can minimize the risk of pesticides, microbes, toxins or residual solvents being accidentally present in retail products.
- Quantification of cannabinoid profiles and potency is needed to determine appropriate dosing for individual use. Overdose, especially due to ingestion of concentrated edible formulations with delayed onset of action, can cause unwanted side-effects.
- Laboratory testing is necessary for cultivators interested in strategic breeding programs.
- Accurate and reliable labels add value to *Cannabis* and *Cannabis*-derived products. Consumers are increasingly concerned about the products they ingest, as demonstrated by the recent public interest in accurate labeling of products as organic and/or non-GMO.
- Laboratory testing provides enhanced legitimacy for the *Cannabis* industry. Physicians may be reluctant to recommend herbal remedies due to concerns about the safety and variability of the products.

The primary role of an analytical *Cannabis* testing laboratory is to guarantee public safety and quality of the products tested. These two goals are attainable when laboratories are accredited, properly managed, participate in regular proficiency testing and quality control practices, and follow valid sampling and testing methodologies. However, *Cannabis* laboratories in the United States are largely unregulated. While some regulators assert that *some* safety testing is better that *no* testing, this assessment may be misguided (Unger 2014). Misleading or unsafe testing of products sold for human use and consumption poses a potential greater public health risk than no testing at all. Many laboratories are run by inexperienced analytical chemists or by non-scientists (Unger 2014). Some laboratories offer tests known to be expensive and time-consuming, at costs that are far less than the reagents themselves (Unger 2014). When given identical samples, laboratories often return results without correlation (Unger 2014). Non-qualified service providers, or “dry labs”, may

outsource analysis or even fabricate results (Miller 2011). Unscrupulous laboratory instrument companies may market equipment to medical *Cannabis* collectives and encourage them to attempt their own testing without appropriate quality controls. Reliable diagnostic testing requires expert laboratory management, including regular quality control, accurate calibration of equipment, and proficiency testing (McPherson 2014). Heterogeneity in *Cannabis* potency, even in flowers obtained from the same individual plant, must also be taken into account with sampling strategies (Sexton and Ziskind, 2013). Sophisticated extraction methods are required for accurate testing of infused products, which may include a variety of matrices found in edible items.

While laboratory testing of *Cannabis* presents unique challenges compared to the analytical testing of other agricultural or pharmaceutical products, there is an internationally accepted infrastructure that regulates analytical testing laboratories around the world: the International Organization for Standardization (ISO). The ISO issues accreditation criteria that are used by both the private sector and governmental regulatory bodies to oversee the laboratories that test food, soil, medicines, and drinking water. Regulators in the State of Vermont can also learn from other state regulations, requirements and experience with *Cannabis* product testing. Best practices for sampling and analytical testing are beginning to emerge, and several *Cannabis* analytical laboratories in the USA recently received ISO 17025 accreditation.

In the sections that follow, we present what we think are the best practices for regulation of *Cannabis* laboratories, in language intended to be accessible and clear. We provide specific recommendations for Vermont regulators (Supplemental Material 1), and provide a detailed rational for these recommendations based on the published literature and the regulations provided by the 23 states and District of Columbia. We review and credit five important papers, that provide hundreds of additional references from the peer-reviewed literature. The first of these, “Standards of Identity, Analysis and Quality Control of *Cannabis*”, was published by editors and scientific consultants for the American Herbal Pharmacopoeia (Upton, 2013). Second, “Sampling Cannabis for Analytical Purposes” was released in August of 2013 by the BOTEC Analysis Corporation (Sexton and Ziskind, 2013). This organization was hired by the state of Washington to consult on the implementation of its recreational *Cannabis* program, and their detailed report addresses sampling procedures for potency testing including financial considerations. Third, BOTEC followed up their report on sampling for potency testing with a comprehensive literature review and recommendations on safety testing, entitled “Testing Cannabis for Contaminants” in Septemeber 2013 (Daley, 2013) Fourth, the “Recommendations for Regulators – Cannabis Operations”, developed by the American Herbal Products Association (AHPA), addresses issues related to the safe use and responsible commerce of legally-marketed products derived from *Cannabis* and includes recommendations for regulators on best practices for laboratory operations (AHPA 2014). Finally, the Cannabis Safety Institute prepared recommendations on standards for *Cannabis* testing laboratories, focusing on safety, in December of 2014 (Unger 2014). We present a financial analysis of the costs for the testing that we recommend (Supplemental Material 2). Finally, we provide additional context by presenting a state-by-state comparison of current laboratory testing requirements, in the 23 states and District of Columbia (Supplemental Material 3). We hope that regulators will follow these recommendations and implement regulations for mandatory testing and labeling of *Cannabis* and *Cannabis*-derived products that prioritize public safety. This will ultimately increase the legitimacy and value of *Cannabis* products and help protect consumers.

II. Laboratory analysis of *Cannabis* for public safety

To meet public health needs, the basic safety testing performed by *Cannabis* laboratories should include methodologies for testing potency and potential contaminants. The categories of testing should at least include the following:

A. Cannabinoids
B. Microbiological Contaminants
C. Residual Chemicals

Best practices for analytical chemistry are typically provided by the AOAC International (http://www.aoac.org) as "official methods of analysis". There are no AOAC official methods of analysis for cannabinoids, but the "Standards of Identity, Analysis and Quality Control of *Cannabis*" published by the American Herbal Pharmacopoeia (AHP) in 2013 provides some guidance (Upton, 2013). The "AOAC International Guidelines for Laboratories Performing Microbiological and Chemical Analyses of Food and Pharmaceuticals" provides recommendations for testing of microbes, toxins, residual solvents, pesticides, and heavy metals. Regulators should not define the specific methods used by laboratories, rather, they should require that laboratories are accredited to the ISO 17025 standard for whichever methods are selected.

A. Cannabinoids

Potency testing of the active ingredients of Cannabis.

Cannabis and *Cannabis*-derived products must be tested by a laboratory for cannabinoid content and potency. Quantification of the cannabinoid profiles and potency of *Cannabis* or *Cannabis*-infused products is needed to determine appropriate dosing for individual use, in order to achieve desired effects. While there are many cannabinoids present in the *Cannabis* plant, at a minimum, the dry-weight percentage of the two predominant active cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD), should be analyzed. The cannabinoid profile should be included on the label of all *Cannabis* and *Cannabis*-infused products. We recommend that potency is reported as the concentration in mg and as the % of product weight with a 95% confidence interval around the point estimate (i.e. 10-12% THC; 0.6 - 0.8% CBD). Determining the profiles of different cannabinoids also provides information for individuals who are increasingly interested in consuming cannabinoids other than THC. The potency of the three most active ingredients in *Cannabis*, delta-9-tetrahydracannabinoid (THC), cannabidiol (CBD) and cannabinol (CBN), varies widely across flowers and extracts prepared from different strains. Cannabinoid profiles are critical in guiding patients and their physicians in selecting strains most suitable for specific ailments. These active ingredients cannot be detected by visual inspection, smell, or other sensory means. Laboratory testing is also critical for cultivators interested in breeding strains that target specific Cannabinoid ratios.

The *Cannabis* plant is inherently variable, with both genetic and environmental contributions that strongly affect the quality of the product. The effect of genetics can be seen when different strains of *Cannabis* are grown and cured under identical conditions. For example, in 44 strains of *Cannabis* cultivated by a medical marijuana dispensary in Vermont for a targeted breeding program, THC content ranged from as low as 2.5% to as high as 18% in samples tested (Figure 1). Only 8 of 44 strains had levels of CBD >3%.

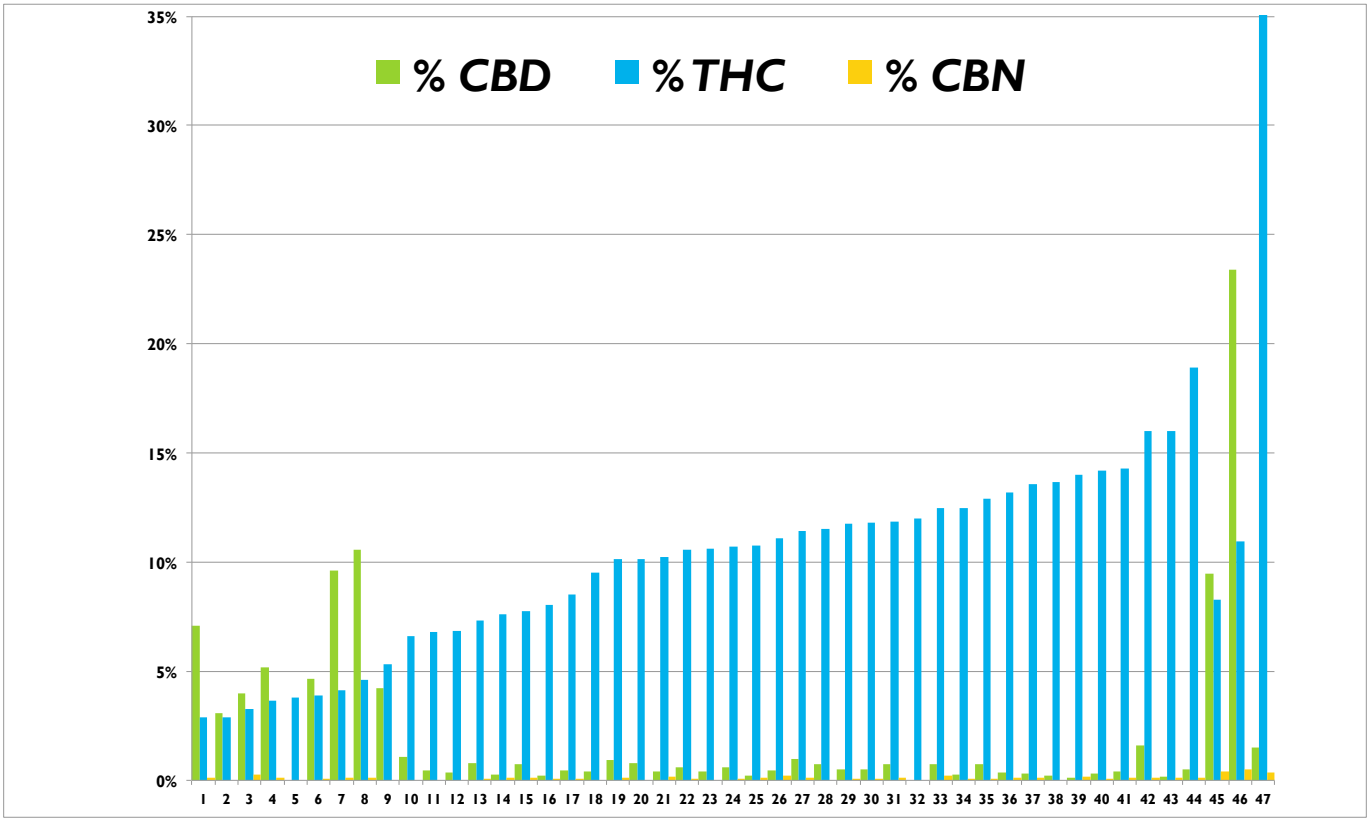
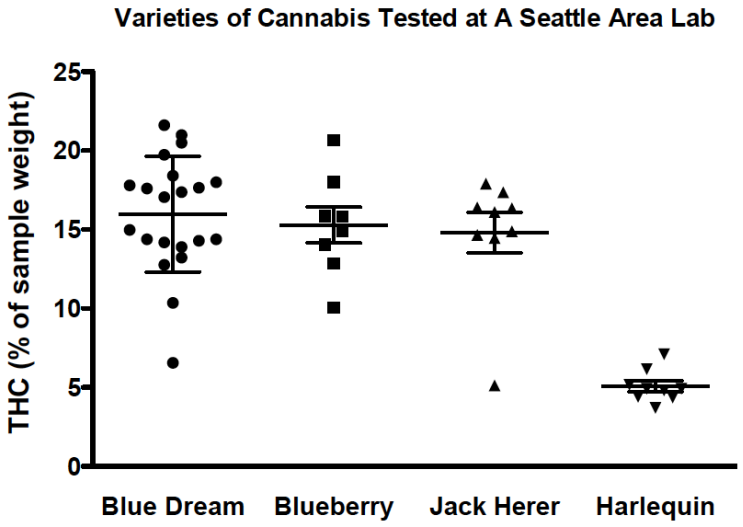


Figure 1. Vermont *Cannabis* strains display a wide range of cannabinoid content and profiles, grow under identical conditions. Forty-four different cultivars of *Cannabis* were obtained from patients in the current Vermont marijuana program (for therapeutic use), and grown under identical conditions. Samples of the dried *Cannabis* inflorescence (1-44) and concentrates (45-47) were analyzed using gas chromatography – flame ionization detection (GC-FID) analysis and compared to commercial standards for CBD, THC, and CBN (Restek Corporation). (Vermont Patients Alliance)

The effects of the environment on quality of the *Cannabis* product can be seen in a comparison of potency within the same *Cannabis* cultivar grown under different conditions. For example in a sample of 47 dried *Cannabis* flowers from 4 different strains, tested under identical conditions in Seattle Washington, the variability within *Cannabis* strains was high (see Figure 2). For example, "Blue Dream" ranged from 6.5 to 21.6% THC as a percent of product weight). Finally, there is even variability in potency within different parts of the inflorescence (flower buds) of the same plant, with the highest potency generally found in the topmost buds. This must be considered in sampling strategies if the sample is to be truly representative of the whole lot (Sexton, 2013).

Cannabis infused food products can include a wide variety of matrices with different chemical compositions that influence the accuracy of potency testing. Therefore, we recommend testing of the extract that is infused into the edible product, prior to infusion, so that the maximum amount of cannabinoids in the product can be calculated and reported on the consumer label. Additionally, for products that are consumed by mouth, rather than by vaporization, the carboxylated or "acid" forms of the psychoactive Cannabinoid THC, THC-A, must also be evaluated. The "acid" forms of THC is not biologically active unless de-carboxylated by heat or chemical extraction, thus it will not have the same effect if ingested by mouth. Labels on products intended for edible consumption should therefore identify the total amount of THC (summation of both THC and THCA) infused, as well as the fraction of THC that is de-carboxylated and therefore an active ingredient.



	Blue Dream	Blue-berry	Jack Herer	Harle quin
# observations	21	8	9	9
Minimum	6.560	10.05	5.130	3.710
25% Percentile	14.05	13.16	14.56	4.385
Median	17.05	15.36	16.11	4.930
75% Percentile	18.20	17.47	16.87	5.670
Maximum	21.61	20.67	17.91	7.110
Mean	15.99	15.27	14.80	5.069
Std. Deviation	3.657	3.206	3.816	1.015
Std. Error	0.798 0	1.134	1.272	0.3385

Figure 2. Potency can vary widely within a particular *Cannabis* strain. Graphical representation and table showing results from 47 samples of *Cannabis* from 4 different cultivars, tested by Analytical 360, a medical *Cannabis* testing laboratory in Seattle. (copied from Sexton, 2013)

Methods for measuring cannabinoids

Cannabinoid analysis using gas chromatography with flame-ionization detection (GC-FID) and high-performance liquid chromatography (HPLC) are both considered valid methods for determination of cannabinoid content in the American Herbal Pharmacopeia recommendations (Upton, 2013). Gas Chromatography requires heat to produce the gas phase, which decarboxylates the acid forms of the cannabinoids, and therefore provides a result representing the sum of THC, which most closely reflects the maximum amount of THC potentially yielded when heated. High Performance Liquid Chromatography (HPLC) is considered the best testing methodology for quantifying cannabinoids if the desired outcome is to know the amount of both THCA and THC in the compound before the product is heated. HPLC is able to distinguish naturally occurring acid and neutral compounds, which is important for *Cannabis*-infused edible products that will not be heated.

For each analytical method, the American Herbal Pharmacopeia recommendations provides detailed best-practiced procedures for accurate testing (Upton, 2013). However, it is important to remember that scientific

methods are constantly evolving. ISO 17025 accreditation does not restrict testing labs to a specific methodology when technology is rapidly improving in the industry, but rather, affirms the reliability of the methodology selected by the laboratory. Regulators should not legislate specific laboratory methodology, as long as the laboratory can achieve accreditation to the standards of ISO 17025 (this validation is described in section on laboratory standards).

B. Microbiological Contaminants

The presence of microbes is common in all natural products. Microbial and fungal values are not typically reported on a pass/fail basis. Rather, acceptable limits are established for a plant produced under normal cultivation conditions. Plants that possess a high concentration of trichomes, such as *Cannabis* or mint (*Mentha* spp.) are especially prone to mold. This should be considered when establishing acceptable limits. Fortunately, the causal association between microbiological pathology and *Cannabis* use is extremely rare, especially given the prevalence of exposure. Microbial limits may also not be relevant for many *Cannabis*-infused products and concentrates that are subject to processing before consumption. Infusing, decocting, or extracting *Cannabis* with heat can reduce or eliminate microbiological contamination.

The American Herbal Pharmacopeia (2013) suggested that *Cannabis* products should be subject to the same microbial and fungal limits recommended for orally consumed botanical products in the US (see Table 9 in their publication for thresholds). This recommendation would require extensive testing performed in a specialized microbiology laboratory with cell-culture technology. Some states, such as Alaska and Colorado, have set “zero tolerance” thresholds (< 1 Colony Forming Unit (CFU) for certain microbiological contaminants in *Cannabis* products (Shiga-toxin producing Escherichia coli [STEC], *Salmonella*, and *Aspergillus*), but do not require additional testing for other molds or coliforms. We agree that known pathogens should not be allowed at any level, but a 200 CFU/ gram threshold is more likely to account for the limitaitons of CFU enumeration methods which are less specific than more rigorous genetic tests. Supplemental Material 1, Table S1.1 provides our threshold recommendations for pathogens in *Cannabis* samples.

C. Pesticides, Heavy Metals and Residual Solvents

Pesticides

Pesticide and other chemical use in the Cannabis industry is a hotly debated legal issue. Under the Federal Insecticide, Fungicide, and Rodenticide Act 7 U.S.C. 136 §12(a)(2)(G) it is unlawful for any person “to use any registered pesticide in a manner inconsistent with its labeling.” However, high quality, commercial *Cannabis* cultivation requires pest control strategies to produce high quantity harvests. While there are organic pesticide options, there currently are no pesticides labeled for use on *Cannabis*. Several states have developed regulations to guide producers on pesticide use.

The *Cannabis* industry’s regulators can use the Environmental Protection Agency’s (EPA’s) residue limits for pesticides on other crops, as a starting point for establishing regulatory limits on *Cannabis*. The Food and Drug Administration (FDA) is traditionally responsible for enforcing the EPA’s regulatory limits of pesticides that may legally remain on food. These limits on pesticides left on foods are called "tolerances" in the United States. They are referred to as maximum residue limits, or MRLs, in many other countries. Tolerances are

meant to protect consumers from harmful levels of pesticides in food. The FDA typically collects and analyzes samples of commercial food products to ensure the pesticide residues are below the threshold. Residue data gathered under this regulatory monitoring program are also used for evaluating the extent and significance of pesticide residues in the food supply. Multi-residue methods (MRMs) are used by the FDA on a routine basis, because of their efficiency and broad applicability, especially for analyzing foods of unknown pesticide treatment history. Until the FDA is willing and able to regulate *Cannabis* in the United States, states must develop their own regulatory procedures for the testing of *Cannabis* products for pesticide residues.

We recommend that residue analysis for common pesticides should also be performed. The BOTEC survey of pesticides commonly used in California identified several that are commonly used in other crops (Daley, 2013); they then summarize those chemicals that have established MRLs for specific commodities (not *Cannabis*) (U.S. Environmental Protection Agency, Office of Pesticide Programs, 2012). We agree with their suggestion that testing for these should serve as a starting point for establishing residue tolerance guidelines or limits for *Cannabis*. Specifically, we recommend that 1 of every 10 lots produced under similar conditions, should be sampled and tested for 12 pesticides listed and rejected if it contains levels above the EPA thresholds for other commodities (Supplemental Material 1, Table S1.2).

Heavy Metals

Cannabis has been demonstrated as a potential crop for phytoremediation of polluted soils (Linger, 2005). Phytoremediation suitable crops accumulate heavy metals throughout their tissue. Crops grown for human consumptions with the ability to hyper accumulate heavy metals, such as *Cannabis*, should be tested for the presence of heavy metals before going to market. Regulators in Alaska and Colorado have provided specific thresholds for heavy metals in *Cannabis* and *Cannabis*-derived products, and these thresholds appear reasonable. We recommend that 1 of every 10 lots produced under similar conditions, should be sampled and tested for 12 pesticides listed and rejected if it contains levels above the recommended thresholds (Supplemental Material 1, Table S1.2).

Residual solvents.

Cannabis concentrates are popular among consumers, vary in their methods of administration, and can harbor dangerous hydrocarbon or organic solvents, concentrated levels of pesticides, and/or highly concentrated levels of Cannabinoids. We recommend that each lot of solvent-based *Cannabis* concentrates should be tested for residual solvents prior to being sold. At least 1 milliliter of each lot (< 1 to 10 Liters) should be sampled for testing. The testing should include at a minimum, butanes, hemtanes, benzene, toluene, hexane, and xylenes. Regulators in Alaska and Colorado have provided specific thresholds for residual solvents in *Cannabis* extracts, and these thresholds appear reasonable. We recommend that all lots of solvent-based *Cannabis* concentrates should be sampled, tested and rejected if it contains levels above the recommended thresholds (Supplemental Material 1, Table S1.2).

III. Sampling and lot sizes

Standardized sampling procedures are an integral part of quality testing. Regulations on sampling procedures are necessary to ensure consistency of *Cannabis* and *Cannabis*-derived products. Sampling estimates the characteristics of a whole lot by selecting a representative subset or the whole. A representative sample of

Cannabis can be difficult to obtain for two reasons: 1) *Cannabis* is a plant that has variable levels of Cannabinoids in nature, within a single plant, and among cultivars; and, 2) *Cannabis* is most commonly sold as an intact flower in Vermont. Proper sampling is an important aspect of *Cannabis* testing because it results will be skewed if done dishonestly or improperly. A good example of this bias is THC content is commonly thought to decrease from the apex to the base of the plant (top to bottom). Cultivators may be tempted to test samples from the top of the plant to exaggerate potency and increase retail value. It is important that producers do not knowingly provide laboratories with samples that are not representative. Cultivators and producers should not be permitted to manipulate sampling procedures.There are several ways to ensure that samples are not manipulated and that they are representative of the whole. The best way to address this potential bias is to prohibit cultivators and producers from choosing their own test sample. Trained laboratory personnel, state regulators, or an independent third party licensed for this activity, should choose random samples from each lots of flower or trim gathered into lots for testing. Another option, which we would not consider a "best practice", is to allow producers to choose random samples their own products, under standardized methods, with an affidavit attesting that the samples provided are representative.

Sample sizes need to be representative for analysis of Cannabis inflorescence. Best practice sampling protocols for laboratories suggest homogenization or grinding of the material prior to sampling. However, homogenizing an entire lot (i.e. grinding the entire crop) is not feasible because it will significantly decrease the value of the product. *Cannabis* testing laboratories must therefore use other ways to verify that a sample of the inflorescence is representative of the whole. A possibility is that flower or trim gathered into lots for testing, using criteria for each lot or lot that include (a) products of the same strain, (b) grown under approximately the same conditions with regard to light, moisture, nutrition, CO2 and temperature, (c) flowers of similar bud size, (d) harvested and cured at the same time. The size of the aliquout used for testing will affect confidence in the results. Some authors have recommended up to 10g per 1,000 grams (1%) of the inflorescence should be obtained for testing (Sexton 2013). However, data suggests that >2 g sample per 1,000 grams (<0.5%), is sufficient to provide an acceptable variability of < 5% in cannabinoid measurement (see Figure 3 below). Therefore, we recommend that 2.5 grams per 1,000 grams is the minimum representative sample of the inflorescence taken from a batch of plants, or trim from the flowers, for testing.

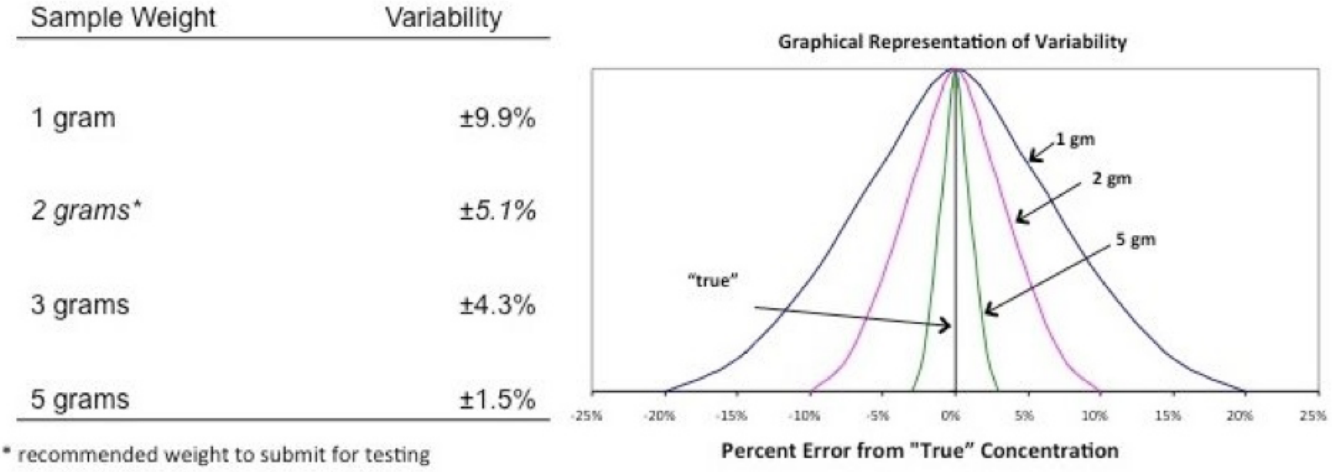


Figure 3. Variability distribution of Cannabinoid potencies when different weights are used in a homogenized sample (copied from Sexton, 2013).

IV. Laboratory standards and best practices

The *Cannabis* testing described above can be accomplished by specialized laboratories. *Cannabis* laboratories should be required to demonstrate competency through the internationally-accepted standards that have been developed for proper analytical laboratory operation. These universal standards have been established for laboratories including those that test drinking water, soil, food and pharmaceutical products. Criteria for competence of such laboratories have been set by the International Organization for Standardization (ISO), in the form of guidelines entitled "General requirements for the competence of testing and calibration laboratories", commonly referred to as ISO 17025. These are complemented by the Organisation for Economic Co-operation and Development (OECD) Principles of Good Lab Practice (GLP), related to the protection of human health and the environment.

High-grade chemical standards for quantification of these cannabinoids are commercially available, along with interlaboratory proficiency testing for cannabinoids have recently become available for Cannabis laboratories across the United States. This now allows regulators to apply the highest level of diagnostic laboratory accreditation to laboratories performing analysis of Cannabis for pubic safety. Several *Cannabis* laboratories in the Unites States were recently accredited to ISO 17025, demonstrating the feasibility of using these criteria to ensure the highest quality in laboratory practice.

We specifically recommend ISO 17025 accreditation for cannabinonids, while acknowledging that there are a variety of other standards for laboratories that have been applied to *Cannabis* laboratories in other states (reviewed in Supplement 3), including the FDA 21 CFR 58 Good Lab Practice for Nonclinical Lab Studies, ANSI-ASQ National Accreditation Board (ACLASS), Clinical Lab Improvement Act (CLIA), National Environmental Lab Accreditation Conference Institute TNI Standards. However, the states, the ISO 17025 standard is the most common required accreditation and others are provided as alternatives. ISO 17025 is the broadest scope of certification in the industry and it is now recognized as the best practice for *Cannabis* testing laboratories. ISO 17025 is applicable to all laboratories regardless of personnel or the scope of testing activities. ISO 17025 covers testing and calibration performed using standard methods, non-standard methods, and laboratory developed methods. The standards are unambiguous and universally accepted. Specifically, regulatory authorities, accreditation bodies, and laboratory customers, use these criteria to confirm the competency of laboratories around the world. ISO 17025 does not mandate what methods a laboratory must use. Rather, the laboratory itself defines those methods that are included within the scope of their accreditation, and each method must be independently verified. If a company has multiple laboratory locations, each individual site must also be independently accredited to ISO 17025. ISO accreditation for a well-run laboratory should be achievable within 6 to 12 months, and third party consultants are available to assist if needed. We discuss specific aspects of laboratory accreditation**,** proficiency testing**,** and management below.

A. Accreditation

Laboratory accreditation to ISO 17025 itself is the formal recognition by an independent third-party of the laboratory's ability to perform specific analytical tests. Laboratory operations may be associated with cultivators, producers, wholesalers, retail stores or medical dispensaries. Whether the *Cannabis* laboratory

itself is "independent" from cultivators and dispensaries is irrelevant to its utility in terms of public health and safety; what matters is that the laboratory *follows ISO 17025 criteria* and *receives accreditation by an independent third-party organization.*

The independent third-party laboratory accreditation system is well established. A mutual recognition arrangement (MRA) among accreditation bodies through the International Laboratory Accreditation Cooperation (ILAC), provides uniform laboratory and inspection accreditation procedures and policies. All ILAC members use ISO 17025 as the basis for testing laboratory accreditation. The accreditation bodies must themselves be recognized as competent through a rigorous peer evaluation process, as detailed by another set of ISO criteria, known as ISO 17011. Accreditation of a *Cannabis* laboratory by an ISO 17011-accredited ILAC member provides assurance that the laboratory produces consistent and reliable results according to ISO 17025 criteria.

Many State and Federal agencies utilize independent third-party accreditation of laboratories as criteria for their recognition, in an efficient private/public partnership. This arrangement allows regulatory authorities to confirm the competence of laboratories, without having to develop entirely new regulatory frameworks. This saves time and resources, allowing regulatory costs to be partly shifted to private parties. As an example, the U.S. Consumer Product Safety Commission depends on ILAC MRA accreditation bodies to accredit those laboratories that test the safety of children's toys, as mandated by the Consumer Product Safety Improvement Act of 2008.

Thus, we recommend that *Cannabis* laboratories performing testing for public safety be certified *at least* for cannabinoid potency measurement (THC and CBD), to ISO 17025, as noted above. This accreditation must be performed by an ISO 17011 accreditation organization. It is feasible for *Cannabis* laboratories in the United States to achieve ISO 17025 accreditation, and in fact, several have already done so.

B. Proficiency Testing

All ISO 17025 accredited laboratories must participate in proficiency testing when it is relevant and available. Regular proficiency testing ensures the reliability of a laboratory's methods, and helps monitor laboratory performance for specific tests or measurements. Proficiency testing requires that the laboratory analyzes one or more samples of unknown composition provided by an independent third party. The laboratory measures the samples according to a given set of instructions and reports the results to the administrator of the test. The results are measured and compared to the reference value of the samples. The third-party organizations which conduct the Inter-laboratory Proficiency Tests (IPT) must also be certified by ISO, under yet another set of standard criteria, ISO 17043.

Because of legal issues that prohibit transporting *Cannabis* across state lines, such proficiency testing has been challenging for *Cannabis* laboratories. In some states, such as California, in-state proficiency testing is possible. More recently, proficiency testing for cannabinoids (but not other measurements) has become feasible and commercially available for *Cannabis* laboratories throughout the United States through ISO 17043 accredited third-party organizations, such as Emerald Scientific. This is achieved by sending cannabinoid samples prepared in solvents to the *Cannabis* laboratories. An example of the results of an acceptable proficiency test

done by the medical *Cannabis* testing lab at Vermont Patients Alliance in Vermont for the cannabinoids cannabidiol (CBD), cannabinol (CBN), and delta-9 tetra-hydro-cannabinoid (THC) is shown in Figure 4.

AbsoluteGrade PT Program ANAB ISO-G34 PT PT Evaluation Report Page 1 of 1

Account # 5024

USEPA Lab ID NA NPDES ID #
Study # QTA Open Date 03/09/2015
Study Type External PT Close Date 03/24/2015

Part# 38368 Lot# 030915 Total THC Medical Cannabis PT 4 components Invoice# 145477 Units ug/mL

NELAC #	Component	Method Code	Method Description	</>	Reported Value	AV or StudyMean	Assigned Value	Acceptance Limits Low	Acceptance Limits High	Performance Evaluation	Analysis Date
N/A	(-)-Delta9-THC					402	402	269	535	NOT REPORTED	
N/A	Cannabidiol	8577	GC-FID		188	201	201	135	267	ACCEPT.	03/23/2015
N/A	Cannabinol	8577	GC-FID		236	241	241	161	321	ACCEPT.	03/23/2015
N/A	(-)-trans-Delta9-THC acid A					160	160	107	213	NOT REPORTED	
N/A	Total (-)-Delta9-THC	8577	GC-FID		510	562	562	377	747	ACCEPT.	03/23/2015

Figure 4. Example of Inter-laboratory Proficiency Tests (IPT) performed in Vermont. Samples of unknown cannabinoid content were sent on ice in the mail and tested for cannabinoids. The values reported by the laboratory are shown, along with acceptance limits and performance evaluation. (Vermont Patients Alliance).

The values reported by the laboratory are compared to an average, or study mean, and the reference (assigned) value. The results are considered "acceptable" if they fall within the acceptance limits. *Cannabis* proficiency testing for detection of pesticides, microbiology, residual solvents, and water activity, are not yet commercially available.

Cannabis testing facilities should analyze proficiency test samples using the same procedures with the same number of replicate analyses, standards, testing analysts, and equipment as used for product testing. Conducting IPT for cannabinoids, at least once per year, is the recommended best practice at this time.

C. Laboratory Management

Managing a successful *Cannabis* testing laboratory requires a high level of training and expertise. Trained technicians can conduct some assays, such as microbiological tests, by following standardized protocols. However, analytical chemistry requires much greater expertise. Specifically, the requirement for accurate cannabinoid extraction and testing in a various food matrices cannot be covered by a simple set of known protocols. Problems may arise due to the interactions between the cannabinoids and the chemicals in different foods, requiring the development of custom buffers and extraction methods for accurate testing. This type of problem solving requires highly-trained scientists with experience in analytical chemistry.

Therefore, *Cannabis* laboratory testing should be overseen by individuals with advanced academic credentials and relevant experience. Minimal qualifications to ensure that a lab is properly managed should be a condition of certification by state regulators. We recommend that *Cannabis* laboratories employ a Scientific Director

with a PhD in a relevant field, or equivalent industry experience in quantitative diagnostic testing (i.e., 3 or more years) of agricultural, food, or pharmaceutical products.

The role of the Scientific Director is to ensure that the *Cannabis* laboratory follows the ISO 17025 criteria, including good lab practices (GLPs), maintaining internal standard operating procedures and quality controls. Instruments should be properly calibrated, maintained, and repaired. *Cannabis* laboratories must establish an adequate chain of custody protocol to store and manage samples. At a minimum, they should be expected to follow criteria for Cannabis laboratories, as recommended by AHPA (subpart 5, section 5.1). The ISO accreditation process will ensure that these criteria are met.

Cannabis laboratories should be treated with the same concerns for public safety as retail or cultivation centers. The state should set limits on the distance of all Cannabis industry buildings are from locations such as schools and day care facilities. All cannabis industry buildings should have state mandated security protocols with entry limited to licensed personnel. Vermont's existing marijuana program (for therapeutic use) requires security features such as video surveillance and off-site monitored alarm systems. State regulators may also need to inspect *Cannabis* laboratories to ensure they are properly secured and follow all state of VT rules governing the testing of *Cannabis*.

V. Financial considerations

A Consideration of financial costs

The total cost for cannabis testing depends on three variables: The sampling requirements (e.g., testing of all lots, versus a 10% random annual sampling of all product); the number of tests required; and the cost per test. Additionally lot size may vary depending on the size of the cultivation facility and their harvesting schedule.

B Financial feasibility

Sampling and testing requirement have significant cost implications. It takes state resources to regulate and monitor quality assurance testing. Significant costs are also levied on the cultivator, producer, or *Cannabis* testing laboratory. Minimizing costs in a regulated *Cannabis* market is important for elimination through competition with the black market. However, it is important to recognize that quality assurance related costs also produce value. Many consumers are willing to pay more for *Cannabis* that can be purchased legally and when they can be assured of potency and purity. Additionally, testing costs will likely decrease over time, as the *Cannabis* industry matures and demand for testing increases.

Requirements for safety and potency testing of *Cannabis* products vary significantly among the states. Those states that have legalized adult-use *Cannabis* – Alaska, Colorado, and Washington – have requirements for product testing. Oregon and the District of Columbia have developed regulations to inspect and certify *Cannabis* testing laboratories. Fourteen states with regulated marijuana programs require some form of quality assurance testing. Eight states that have regulated medical marijuana programs do not require any form of testing, but at least five of these are in the process of developing the regulatory framework for product testing.

It is important to take into consideration the costs incurred by the producer. We have built a financial model (shown in Appendix 2) to calculate the total costs of testing under a variety of scenarios. In the table below, we show the costs of testing for both Models: A) potency only and B) comprehensive testing (potency plus microbial, solvents, heavy metals, etc.).

	Low Price of Product =$5/gr	**High Price of Product = $18/gr**
Model A	$92.50 (1.88%)	$125 (0.70%)
Model B	$402.50 (8.75%)	$435 (2.48%)

Figure 5. Testing costs in total dollars and as a percentage of the value of the product. The cost of testing for 1 kg of product is the same, but the relative cost changes as with the value of the product. We compare two levels of pricing for gram of product (a low price of $5/gram for trim and a high price of $18/gram for premium flower) to show the effect on cost of testing a sample from 1 kg of product. Model A includes potency testing only, Model B includes safety testing for contaminants.

The numbers in Figure 5 assume that the whole sample is destroyed leaving no residual value to the cultivator or producer. Under these assumptions, the cost of sampling and testing a 1 kg lot of *Cannabis* varies from 0.7% to 8.75% of the total value.

We recommend all lots of Cannabis and Cannabis-derived products must be tested for potency (Model A), but only 10% of lots must also be tested for contaminants (Model B) - as long as the lots were produced under similar conditions.

We ran an additional simulation representing a typical small commercial operation with 6 crops per year, 24 lights of 1000 watts each, 4 plants per light, of 10 different strains for a total of 96 plants. We assume further that each strain will yield 2.5 lbs under these conditions, for a total yield of 25 lbs or more or less 10 kgs per crop. We assume that all 10 kgs of each strain will be tested separately for potency and only one of them randomly selected to be tested for “everything” including contaminants. We calculate the costs to the producer at two levels 5$ and $18 per gram. Under these recommendations, according to our model, the cost to the producer ranges from .87% to 2.53% of the total value of the product.

Detailed information and assumptions are provided in Supplemental Material 2.

Supplemental Material 1: Specific Recommendations for Regulators

Subpart A – General provisions
- Section A.1 Subject operations
- Section A.2 other statutory provisions and regulations
- Section A.3 Definitions

Subpart B – Laboratory testing for public safety
- Section B.1 Scope of laboratory functions needed for public safety
- Section B.2 Thresholds for contaminants
- Section B.3 Consumer labels

Subpart C – Personnel, facilities, and security
- Section C.1 Personnel
- Section C.2 Facilites
- Section C.3 Security

Subpart D – Sample receipt, handling, and disposition
- Section D.1 Sample receipt
- Section D.2 Cannabis plant material
- Section D.3 *Cannabis*-extracts (liquids or oils)
- Section D.4 *Cannabis* solids and semi-solids
- Section D.5 *Cannabis*-infused food products

Subpart E – Laboratory operations, analysis, and reporting of samples
- Section E. Laboratory operations

Subpart F – Regulatory guidance
- Section F.1 *Cannabis* Scientific Advisory Council
- Section F.2 *Cannabis* Science Research Grant Program

NOTE: These recommendations for Cannabis laboratory operations were prepared by the Phyto Science Institute, with the intent of establishing a basis for oversight of entities performing laboratory analysis of Cannabis and Cannabis-infused products. The recommendations are intended to complement existing laboratory best practices and ISO 17025 guidelines, with details on management, personnel, security, sample handling and disposal, data management and reporting activities that may be unique to Cannabis diagnostic laboratories. These recommendations are based on those provided by the American Herbal Products Association (www.ahpa.org), our own experience, a comprehensive evaluation of the published literature, and a detailed review of current Cannabis legislation in 23 States and the District of Columbia. To facilitate the utilization of these recommendations by regulators in the State of Vermont, they are presented in the form of draft regulations.

SUBPART A – GENERAL PROVISIONS

Section A.1 Subject operations
(a) Provisions regarding *Cannabis* testing for public safety apply to retail sales of all *Cannabis* and *Cannabis*-derived products, including marijuana, hemp and their extracts that are intended for human consumption.

(b) "Laboratory operations" apply to any person, group of persons, non-profit entity, or business entity licensed by the State to perform analytical testing of *Cannabis* or *Cannabis*-derived products for safety and potency.

Section A.2 Statutory provisions and regulations
Laboratory operations must comply with all other applicable statutory provisions and regulations related to cannabis laboratory operations in the State, and related to all other business activities undertaken in conducting a laboratory operation.

Section A.3 Definitions
Throughout the paper, the following definitions apply:

- *Analyte* means a specific compound or chemical that is being tested.
- *Cannabis* means any of the aerial parts of a plant in the genus *Cannabis*, including both marijuana and hemp.
- *Cannabis-derived product* means a product, other than *Cannabis* itself, which contains or is derived from *Cannabis*, and does not mean a product that contains or is derived from hemp.
- *Cannabis waste* means *Cannabis* or *Cannabis* -derived product discarded by a laboratory operation.
- *Compliant business* means a business that has met all legal requirements to obtain, possess, manufacture, distribute, or sell *Cannabis* and *Cannabis* -derived products in the jurisdiction where this part applies.
- *Compliant individual* means an individual who has met all legal requirements to obtain and use *Cannabis* or *Cannabis* -derived products in the jurisdiction where this part applies.
- *Controlled access area* means an area in a laboratory facility designed to physically prevent entry by anyone except authorized personnel.
- *Hemp* means any part of a plant in the genus *Cannabis*, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 (three-tenths) percent on a dry weight basis.
- *Hemp-derived product* means a product, other than hemp itself, which contains or is derived from hemp.
- *Laboratory facility* means the physical location(s) of a laboratory operation.
- *Laboratory operation* means a person, group of persons, non-profit entity, or business entity that conducts analytical testing of cannabis, cannabis-derived products, hemp, or hemp-derived products.
- *Lot or batch* of *Cannabis* inflorescence is a collection of the same strain or cultivar up to 1 kg in dry weight that is grown, harvested and cured at the same time. For infused products, a lot or batch is defined as a formulated quantity manufactured at the same time using identical methods and materials, up to 500 ml in volume.
- *Macroscopic examination* means using the naked eye or minor magnification (e.g., with a 10x magnifying glass) to observe and/or measure a sample or object.

- *Marijuana* means any part of a plant in the genus *Cannabis*, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of more than 0.3 (three-tenths) percent on a dry weight basis.
- *May* is used to indicate an action or activity that is permitted.
- *Microscopic examination* means using a microscope to view samples and objects that cannot be seen with the unaided eye (objects that are not within the resolution range of the normal eye).
- *Must* is used to state a requirement.
- *Organoleptic examination* means testing by using sense organs to evaluate flavor, aroma, appearance, or texture.
- *Primary reference standard* means a reference standard whose purity is determined with a high degree of confidence through comprehensive analysis using multiple test methods based on differing principles, such as HPLC or GC, MS, NMR, Karl-Fisher, etc.
- *Purity* means the relative freedom from extraneous matter, contaminants, or impurities, whether or not harmful to the consumer or deleterious to the product.
- *Secondary reference standard* means a reference standard whose purity is established by assaying it against a primary standard.
- *Should* is used to state recommended or advisory procedures.
- *Strain or cultivar* is used to refer to a group of plants of the same species that have been cultivated for particular genetically-encoded tendencies, such as cannabidiol (CBD) production.
- *Strength* means the potency of cannabis or a cannabis-derived product, whether expressed as (a) the amount or percent of specific chemical constituents or groups of chemical constituents; (b) the concentration or amount of cannabis present in a cannabis-derived product; or (c), in the case of cannabis extracts, the ratio of the input quantity of crude cannabis, on a dry weight basis, to the output quantity of finished extract.
- *Test sample* means the specific portion of cannabis, cannabis-derived product, hemp, or hemp-derived product submitted for analysis.
- *Volumetric solution* means a solution used for volumetric analysis, such as titration, wherein the content of analyte is determined by reacting the analyte with a known quantity of standardized reagent.

SUBPART B – LABORATORY TESTING FOR PUBLIC SAFETY AND HEALTH

Section B.1 Scope of laboratory functions

(a) To ensure public health and safety, representative samples of each lot or batch of *Cannabis* and *Cannabis*-derived products intended for human consumption must be tested for safety and potency.

(b) A lot or batch of *Cannabis* inflorescence is defined as a collection of *Cannabis* of the same strain or cultivar *up to 1 kg in dry weight* that is grown, harvested and cured at the same time. For *Cannabis*-infused products, a lot or batch is defined as a formulated quantity manufactured at the same time using identical methods and materials, *up to 500 ml in volume*.

(c) *Samples from each lot* of *Cannabis* or *Cannabis*-derived products must be tested for the potency (total amount in milligrams) of the predominant active ingredients

(1) Tetrahydrocannabinolic acid (THC-acid);

(2) Delta-9 tetrahydrocannabinol (Δ9 THC);

(4) Cannabidiol (CBD);

(d) *Samples from 1 out of every 10 lots* of *Cannabis* or *Cannabis*-derived products must be tested for the most

likely contaminants

(1) Microbiological organisms (pathogenic bacteria and fungus)
(2) Pesticides
(3) Heavy metals

(e) *Samples from each lot* of *Cannabis*-extract prepared with hydrocarbon or organic solvents must *also* be tested for residual solvents.

Section B.2 Thresholds for contaminants

(a) *Microbial contaminants.* All samples of *Cannabis* and *Cannabis*-derived products must be certified to be above the thresholds provided for pathogenic microbiological contaminants including Shiga-toxin producing *E. Coli*, *Salmonella*, and *Aspergillus* measured as colony forming units/ gram. Testing for these three categories of contaminants does *not* exclude all possible fungi or the residual toxins that they may produce, but this level of testing is a reasonable first step, consistent with recommendations provided for adult-use *Cannabis* in Alaska and Colorado.

Table S1.1. Recommended acceptable thresholds for microbiological contaminants in *Cannabis* or *Cannabis*-infused products.

Pathogen	Acceptable Limits Per Gram
Shiga-toxin producing *Escherichia coli* (STEC) – Bacteria	< 200 Colony Forming Unit (CFU)/g
Salmonella species – Bacteria	< 200 Colony Forming Unit (CFU)/g
Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger – Fungus	< 200 Colony Forming Unit (CFU)/g

Along with microbes, it is possible toxins produced by those microbes may be present. While full mycotoxin testing of *Cannabis* is possible, thresholds for toxicity have not been established. From a technical standpoint, if all *Cannabis* samples were subjected to mycotoxin testing, it is expected that 99 to 100% percent of them would show some trace of mold spores, as they are nearly omnipresent on all living things. The question then is: What is the acceptable threshold for human consumption of mold spores or toxins? If the consumed Cannabis is vaporized or smoked (i.e., heated at high temperatures), the threshold for the acceptability of spores or mycotoxin on cannabis is likely to be much higher than that of food products, water supplies or medical equipment. In the absence of established thresholds for mycotoxin toxicity, we do not recommend testing for mycotoxins at this time. Rather, at this time we recommend testing for the total mold and yeast content at the threshold determined by the American Herbal Products Association of 200,000 CFU/ g.

(b) *Pesticides.* Samples of *Cannabis* and *Cannabis*-derived products must be tested to demonstrate that levels of common pesticides are above toxic thresholds (Table 2). It is not feasible to test samples for all possible chemical pesticides or growth modulators. In a recent survey, BOTEC identified hundreds of chemicals including insecticides, acaricides, and fungicides used by growers of medical *Cannabis* in California (Daley, 2013). Some of these are common horticultural products or additives that are exempted from tolerance regulation (e.g. mineral oils) because they are generally regarded as safe. Because *Cannabis* is a high value

crop, there is a risk that some growers will use potentially toxic methods to maximize yields. Appropriate registrations and inspections of growers for pesticide use should therefore be implemented by the Department of Agriculture. This is important to protect not only consumers from trace residues, but also to protect workers engaged in production and the environment.

Until the Department of Agriculture develops comprehensive recommendations of approved pesticides for Cannabis cultivation, and a regulatory system for ensuring adherance to these guidelines, we recommend that residue analysis for common pesticides should also be performed. This may be unnecssary in the future, but such testing is feasible at least for a fraction of chemicals that are known to be toxic in other agriculture commodities.

Residue limits for pesticides that may remain in or on food, feed products, and commodities are called "tolerances" or "maximum residue limits" (MRLs). The BOTEC survey of pesticides commonly used in California identified several that are commonly used in other crops (Daley, 2013); including established MRLs for specific commodities (U.S. Environmental Protection Agency, Office of Pesticide Programs, 2012). These should serve as a starting point for establishing residue tolerance guidelines or limits for *Cannabis*.

There are a variety of methods to demonstrate that samples contain levels of pesticides below these limits. Multi-residue methods can screen for multiple pesticides simultaneously for a relatively low cost.

Table S1.2. Recommended acceptable thresholds for 12 pesticides used in *Cannabis* production based on the EPA's maximum residue limits for these pesticides on other crops (U.S. Environmental Protection Agency, Office of Pesticide Programs, 2012) were complied by BOTEC (Daley, 2013) and are reproduced here. All values are in parts per million (ppm).

Primary Active Ingredient	Lettuce	Spinach	Spearmint	Berry	Cherry	Strawberry	Vine fruit	Wheat grain	Hops	Nuts	Dry herbs
acephate	10		27								
acequinocyl				0.5	0.5		1.6		4	0.02	
avermectin	0.1		0.01			0.02			0.2	0.01	0.03
bifenazate			25	15	5	1.5	1		15	0.2	
diazinon	0.7		0.7		0.2	0.5	0.75			0.5	
ethephon				20-30	10			2		0.5-0.8	
etoxazole			10	0.5						0.1	
imazalil								0.1			
imidacloprid	3.5	3.5		0.5-3.5		0.5		0.05	6	0.05	48
myclobutanil		0.03	3	20-30	5			0.03	10		
pyrethrins				1	1			3		0.02-1	
spinosyn		8	3.5	0.01-0.7		1			22		22

(c) *Heavy metals.* Samples of *Cannabis* and *Cannabis*-derived products must be certified to be above the thresholds for heavy metals provided in Table S1.3, based on regulations in place in Alaska and Coloroado.

Table S1.3. Recommended limits for heavy metals in *Cannabis* and *Cannabis*-derived products.

Substance	Acceptable Limits Per Gram
Metals (Arsenic, Cadmium, Lead, and Mercury)	Lead - Max Limit: < 10 ppm Arsenic - Max Limit: < 10 ppm Cadmium - Max Limit: < 4.1 ppm Mercury - Max Limit: < 2.0 ppm

(d) *Residual solvents / volatile organic compounds*. *Cannabis* extracts made with hydrocarbon or organic solvents must also be tested for residual solvents, or volatile organic compounds (VOCs). The testing should include at a minimum, butanes, heptanes, benzene, toluene, hexane, and xylenes and samples should be certified that the contain levels below the acceptable thresholds, below (Table 4).

Table S1.4. Recommended acceptable limits for residual solvents to be tested in concentrated retail *Cannabis* products made using solvent extraction techniques.

Substance	Acceptable Limits Per Gram
Butanes	<800 Parts Per Million (PPM)
Heptanes	< 500 Parts Per Million (PPM)
Benzene**	< 1 Parts Per Million (PPM)
Toluene**	< 1 Parts Per Million (PPM)
Hexane**	< 10 Parts Per Million (PPM)
Total Xylenes (m, p, o-xylenes)	< 1 Parts Per Million (PPM)
Any solvent not permitted for use	None detected

Section B.3 Consumer labeling

The Fair Packaging and Labeling Act (FPLA or Act), enacted in 1967, enables the Federal Trade Commission and the Food and Drug Administration regulate that all "consumer commodities" be labeled to disclose net contents, identity of commodity, and name and place of business of the product's manufacturer, packer, or distributor. The purpose of the FPLA is to facilitate value comparisons and to prevent false (deceptive or unfair) labeling of consumer commodities. The Food and Drug Administration (FDA) administers the FPLA with respect to foods, drugs, cosmetics, and medical devices. The FPLA requires that each package is labeled with: 1) a statement identifying the commodity; 2) the name and place of business of the manufacturer, packer, or distributor; and 3) the net quantity of contents in terms of weight, measure, or numerical count (measurement must be in both metric and inch/pound units).

The FDA does not regulate Cannabis commodities, and without this regulation states should regulate labels for *Cannabis* products. We recommend the state of Vermont requires each packaged is labeled with: 1) a statement identifying the commodity including the particular strain(s) of *Cannabis*; 2) the name and place of business of the cultivator, producer, or distributor, and the retail store; 3) the weight of *Cannabis* contained

within the package in grams; 4) ingredients added during preparation if not raw plant material; 5) amount of THC and CBD; 6) dosage, serving size and numbers of servings/package; and 7) safety handling and storage instructions.

SUBPART C – PERSONNEL, FACILITIES, AND SECURITY

Section C.1 Personnel

(a) Management. The laboratory must be managed by a qualified laboratory director with a PhD or equivalent such as 3 or more years of industry experience in scientific methods including quantitative diagnostic testing.
(b) Personnel. Each person engaged in the laboratory operation must be undergo a background check and receive credentials from the state for such activities.

Section C.2 Facilities

Laboratory operations must be operated in adherence with any regulation in the State that is relevant to its specific operations, including appropriate distance from schools or playgrounds.

Section C.3. Security

(a) Laboratory operations must establish and adhere to such security procedures applicable by State regulations for *Cannabis*.
(b) Laboratory operations should:

(1) Provide additional security as needed to protect the employees during working hours and in a manner appropriate for the community where it operates; and
(2) Provide training to make all employees aware of the operation's security procedures, and each individual employee's security roles and responsibilities.

(c) Laboratory operations must be equipped with one or more controlled access areas for storage of the following:

(1) *Cannabis* and *cannabis*-derived test samples;
(2) *Cannabis* waste; and
(3) Reference standards for analysis of cannabinoids.

(d) Access to controlled areas must be limited by locks, electronic badge readers, biometric identifiers, or other means.
(e) Appropriate steps must be taken to ensure access privileges to the laboratory facility and to controlled access areas, as applicable, are revoked for personnel who are no longer employed by the operation.
(f) There must be written procedures for security.

SUBPART D – SAMPLE RECEIPT, HANDLING, AND DISPOSITION

Section D.1 Sample receipt

(a) Laboratory operations may be contracted to collect test samples on behalf of any compliant business or compliant individuals
(b) Laboratory operations should establish and implement policies for:

(1) Collecting test samples in a manner that ensures that the test sample accurately represents the material being sampled, to assure that all testing can be accomplished, and an appropriate amount

retained so that further retesting can be done when necessary. A structured process whereby any portions of the matrix taken, are intrinsically identical in all properties to the bulk matrix, allowing that further analytical portions will contain the same intrinsic properties as the original sample.

(2) Other parameters affecting sample preparation, documentation, and transport, including, if applicable:

(i) Accepted test sample types;
(ii) Minimum test sample size;
(iii) Recommended test sample containers;
(iv) Test sample labeling;
(v) Transport and storage conditions, such as refrigeration if required;
(vi) Other requirements, such as use of preservatives, inert gas, or other measures designed to protect sample integrity; and
(vii) Use of sample chain of custody forms.

Section D.2 *Cannabis* plant material

(a)Sampling: Finished plant material is dried and trimmed *Cannabis* inflorescences (i.e. "bud") or trim. Finished product can be directly consumed without further processing. A sample should be tested that is representative in maturity and composition of the production "lot". A lot is finished plant material that was grown at the same time, using the same methods, equipment and ingredients. We recommend that samples of at least 2.5 grams from each lot of flower buds (up to 1 kg / lot) should be set aside for testing. Sampling should take place after the material has been dried, trimmed, cured and/or processed.

(b) Homogenization of samples: The finished plant material should be ground to make sure it is homogenous. Quartering is the standard method used to make sure the sample is homogenous and representative. The sample is mixed and then divided into four equal quarters. Samples from two of the quarters are selected and tested for potency. The remaining quarters are combined and tested for microbiological and contaminant testing. Homogenization is defined as: A structured process whereby any portions of the matrix taken, are intrinsically identical in all properties to the bulk matrix, allowing that further analytical portions will contain the same intrinsic properties as the original sample.

(c) Testing of THC and CBD Potency: At least 2.5 grams sampled from each lot should be tested for potency of THC and CBD. This is the minimum sampling requirement to ensure variability <5% in results. Results should be reported as the 95% confidence interval around the potency point estimate.

(d) Testing for Microbiological pesticide, and heavy metal contaminants: Samples should be tested for microbiological, pesticide and heavy metals contaminants. If multiple lots of flower buds are grown under the same conditions, only one out of every 10 (105) of those samples tested for potency need to be tested for contaminants. Results should be reported as "acceptable" or "unacceptable" with based on falling above or below the permitted threshold limits.

Section D.3 *Cannabis*-extracts (liquids or oils)

(a) Sampling: At least 2 ml from each lot (up to 1 L) of extract should be set aside for testing.

(b) A simple and common protocol can be used for sampling *Cannabis* liquids, such as oil or tinctures. The liquid should be thoroughly stirred or mixed before sampling to make sure it is homogenous. The liquid should be sampled in units of volume.

(c) We recommend taking at a minimal the dose amount from a well-mixed product and diluting into the extraction solution 1:49 as above and mix well then make further dilutions in running buffer for analysis.

Section D.4 *Cannabis* solids and semi-solids

(a) Solids such as Cannabis resin should be ground and thoroughly mixed before it is tested. Cannabis resin is made by separating the trichomes from the finished plant material. Resins and other solids should be ground by a method that minimize loss, such as leaching resins from finished plant material.
(b) As with finished plant material, the quartering method should be used to obtain representative samples for testing. Solids and other resins should not be melted to homogenize. Heating can alter the cannabinoid profile and make the sample unrepresentative. Some *Cannabis* products will require subsamples to be properly tested. If possible, subsamples should be combined and mixed to achieve an amount needed for analysis. It may be difficult to composite subsamples of some products, such as *Cannabis* lozenges. If so, individual units should be provided to the *Cannabis* testing facility for analysis.

Section D.5 *Cannabis* infused food products

All extracts should be tested as above prior to infusing in food. Once infused into food, the resulting product should be regulated by additional FDA standards (shelf life, storage, safety, etc.).

SUBPART E - LABORATORY OPERATIONS, ANALYSIS, AND REPORTING OF SAMPLES

Section E. Laboratory operations

(a) Laboratory operations that perform testing of *Cannabis* for public safety must be licensed by the State and accredited to the ISO 17025 standard by an International Laboratory Accreditation Cooperation (ILAC) third-party body with ISO 17011 credentials. All aspect of laboratory operations shall also be compliant with Current Good Laboratory Practices and Facilitates Management of (cGLP) guidelines. Specifically, laboratory operations; sampling and disposal protocol; handling of equipment, solutions, reagents and standard; analysis of samples (procedures and recording); and, data handling (review, storage, reporting) shall all be performed in such a way as to comply with the most recent ISO 17025 and cGLP standards.
(b) The ISO 17025 accreditation is awarded to laboratories for specific methods; to be licensed to perform testing for public safety, labs must *at least* have ISO 17025 accreditation for analytic measurement of the most important biologically active cannabinoids: THC and CBD. Laboratories should also demonstrate ongoing proficiency in testing for THC and CBD through annual interlaboratory proficiency testing.
(c) Laboratory operations must be housed in secure facilities fulfilling the same security requirements defined by the State for retail, production, and cultivation.
(d) Laboratories must be supervised by a qualified scientist with a PhD or equivalent industry experience (i.e., 3 or more years), in quantitative testing of *Cannabis*, agricultural, food, or pharmaceutical products.
(e) Laboratory operators may be associated with cultivators, producers, wholesalers, retail stores or medical dispensaries as long as they are licensed by the State and accredited to the ISO 17025 standard for testing of cannabinoids by an International Laboratory Accreditation Cooperation (ILAC) third-party body.

SUBPART F – REGULATORY GUIDANCE

Section F.1 *Cannabis* Scientific Advisory Council.
We recommend that Vermont establishes a *Cannabis* Scientific Advisory Council with appropriate credentials and experience. The Council would be responsible for the following scope of work:
(a) Establishing approved methods of cannabinoid extraction (e.g., super-critical CO_2 extraction, Rick Simpson Oil) and *Cannabis*-derived product manufacturing;
(b) Setting thresholds for acceptable levels of contaminants;
(c) Determining criteria for product recall; and,
(d) Provide policy guidance in the creation and implementation of the *Cannabis* science research grant program and its scientific oversight and review.

Section F.2. Cannabis Science Research Grant Program
We recommend that Vermont establishes a *Cannabis* Science Research Grant program to meet the need for objective scientific research. Specifically:
(a)The State should set aside 5% of tax revenue from *Cannabis* sales to establish *Cannabis* Science Research Grant program.
(b) Grants should be awarded to Investigators at Vermont Colleges, Universities, and private companies studying *Cannabis;* grants should be administered by their sponsored programs offices or research and development departments; academic partnerships with industry may be encouraged to advance the development of science and technology.
(c) The size, scope, and number of studies funded shall be commensurate with the amount of appropriated and available grant program funding.
(d) The *Cannabis* Scientific Advisory Council shall evaluate research proposals in a peer-review process that guards against funding research that is biased in favor of or against particular outcomes.

(1) The Council shall submit recommendations to the regulatory department for recommended grant recipients, grant amounts, and grant duration. The regulatory department shall approve or disapprove of grants submitted by the Council. If the regulatory Department disapproves a recommendation, the Council may submit a replacement recommendation within thirty days.

(2) The state board shall award grants to the selected entities, specifying the amount and duration of the award. A grant awarded pursuant to this section shall not exceed three years without renewal.

Supplemental Material 2: Financial models

Table S2.1. Model of cost per gram for safety testing. The cost is a function of the price per gram of product and # tests required and. Assumptions are listed as "given" including costs for specific test batteries.

Cost of product per gram, Cp (expressed in $)							
Sample size, variable Sz (in grams)							
Amount of sample that gets destroyed in the process, variable Sd (in %)							
Amount returned to producer as a by-product, variable Sb (in grams)							
Value of by-product Sb per gram, Vb (in $)							
Cost of potency test is variable Ct (in $)							
Cost of microbial analysis (total counts fo rmicrobes and yeast) is avriable Cmi (in $)							
Cost for test of solvents is variable, Cso (in $)							
Cost of heavy metal is variable Chm (in $)							
Cost of Multiresidue Methods (MRM) for unknown pesticides is variable Cmrm (in $)							
Total cost to producer is cost of the destroyed and reduce value product and the cost of testing sample (in $)							
Total number of kilos of product, variable P (in thousands of grams)							
Total cost of testing as a percentage of value, variable TCv							
Scenario 1: Price per gram $18, all tests			Scenario 2: Price per gram $18, only potency test				
Cp	$18.00	given	Cp	$18.00	given		
Ct	$80.00	given	Ct	$80.00	given		
Cmi	$70.00	given	Cmi	$0.00	given		
Cso	$120.00	given	Cso	$0.00	given		
Chm	$20.00	given	Chm	$0.00	given		
Cmrm	$100.00	given	Cmrm	$0.00	given		
Sz	2.5	given	Sz	2.5	given		
Sd	100%	given	Sd	100%	given		
Sb	0%	calculated from above	Sb	0%	calculated from above		
Vb	$9.00	given	Vb	$9.00	given		
P	1	given	P	1	given		
Tc	$435.00	calculated from above	Tc	$125.00	calculated from above		
TCv	2.48%	calculated from above	TCv	0.70%	calculated from above		
Scenario 3: Price per gram $5, all tests			Scenario 4: Price per gram $5, only potency test				
Cp	$5.00	given	Cp	$5.00	given		
Ct	$80.00	given	Ct	$80.00	given		
Cmi	$70.00	given	Cmi	$0.00	given		
Cso	$120.00	given	Cso	$0.00	given		
Chm	$20.00	given	Chm	$0.00	given		
Cmrm	$100.00	given	Cmrm	$0.00	given		
Sz	2.5	given	Sz	2.5	given		
Sd	100%	given	Sd	100%	given		
Sb	0%	calculated from above	Sb	0%	calculated from above		
Vb	$9.00	given	Vb	$9.00	given		
P	1	given	P	1	given		
Tc	$402.50	calculated from above	Tc	$92.50	calculated from above		
TCv	8.75%	calculated from above	TCv	1.88%	calculated from above		

Table S2.2. Model of cost of testing for a commercial *Cannabis* growing operation in Vermont, according to our recommendations of testing all batches for potency and 10% for contaminants. Assumptions are listed, including a 24 x 1000 watt indoor grow room with 10 strains of Cannabis, 96 plants, and a crop yield of 10 equal batches or lots (one for each strain) that totals approximately 10kg.

Assume:		
6 crops per year		
24 lights x1000watts (indoor grow)		
4 plants per light, 10 strains total (96 plants)		
2-2.5lbs per each strain = 1 kg lots		
20-25lbs total yield= +/- 10 kgs total		
10x 1kg, 2.5g of each tested for potency.		
One of these 10 is selected at random for everyting test no extra sample needed		
Cost of product per gram, Cp (expressed in $)		
Sample size, variable Sz (in grams)		
Amount of sample that gets destroyed in the process, variable Sd (in %)		
Amount returned to producer as a by-product, variable Sb (in grams)		
Value of by-product Sb per gram, Vb (in $)		
Cost of potency test is variable Ct (in $)		
Cost of microbial analysis (total counts fo rmicrobes and yeast) is avriable Cmi (in $)		
Cost for test of solvents is variable, Cso (in $)		
Cost of heavy metal is variable Chm (in $)		
Cost of Multiresidue Methods (MRM) for unknown pesticides is variable Cmrm (in $)		
Total cost to producer is cost of the destroyed and reduce value product and the cost of testing sample (in $)		
Total number of kilos of product, variable P (in thousands of grams)		
Total cost of testing as a percentage of value, variable TCv		

Scenario 1: Price per gram $18			Scenario 2: Price per gram $5		
Quantity	10 lots of 1 kg		Quantity	10 lots of 1kg	
Cp	$18.00	given	Cp	$5.00	given
Ct	$80.00	given	Ct	$80.00	given
Cmi	$70.00	given	Cmi	$70.00	given
Cso	$120.00	given	Cso	$120.00	given
Chm	$20.00	given	Chm	$20.00	given
Cmrm	$100.00	given	Cmrm	$100.00	given
Sz	2.5	given	Sz	2.5	given
Sd	100%	given	Sd	100%	given
Sb	0%	calculated from above	Sb	0%	calculated from above
Vb	$9.00	given	Vb	$9.00	given
P	10	given	P	10	given
Tc	$1,560.00	calculated from above	Tc	$1,235.00	calculated from above
TCv	0.87%	calculated from above	TCv	2.53%	calculated from above

Supplemental Material 3 Comparison between states

Table S3. State-by-state comparison of regulatory requirements for laboratory testing of *Cannabis* and *Cannabis*-derived products (updated November 2015).

State	State Certification	Testing Requirements	Accreditation/ Lab Requirements	Sampling
AK (Adult use)	Yes. Labs must be licensed by the Alcohol Control Board. Legislature may create a Marijuana Control Board over time.	Required: i. Harmful microbial including E. coli or salmonella ii. Potency (THC, THCA, CBD, CBDA, CBN) iii. Residual solvents Labs must also be capable of performing the following testing: 1. Poison or toxin 2. Harmful chemical 3. Dangerous molds, mildew, or filth 4. Pesticide, herbicide and fungicide	No accreditation required. Must adopt specific testing methodologies: 1. UNODC 2. American Herbal Pharmacopoeia Other requirements. 1. Proficiency testing may be required. 2. Qualified scientific director 3. Standard operating procedure Must also integrate good lab practices to the extent possible: 1. FDA in 21 CFR 58 Good Lab Practice for Nonclinical Lab Studies 2. OECD Principles of Good Lab Practice and Compliance Monitoring	Random, homogenous sample. lots cannot exceed 5 pounds.
CO (Adult use)	Yes. Labs must be licensed by the Marijuana Enforcement Division (MED) within the Department of Revenue.	Required: 1. Potency 2. Microbial 3. Visibly inspect for mold, mildew, filth 4. Residual solvents for concentrates	No accreditation required. Lab requirements: 1. Successful onsite inspection 2. Proficiency testing 3. Ongoing compliance with regulations	Cultivators and manufacturers must test samples for at least 10% of lot it produces on annual basis. Division approved sampled must collect samples. Specific number of samples required based on pounds in lot.
CT (Medical)	No. Labs are not state licensed. Department of Consumer Protection regulates MMJ program.	1. Microbiological contaminants 2. Mycotoxins 3. Heavy metals 4. Pesticide chemical residue 5. Terpene profile and active ingredient analysis	No accreditation required. Lab requirements: 1. Must be registered as a controlled substance lab 2. Must be independent 3. Qualified lab director	Homogenized sample from each lot. Lot size not set in regulations.
DC (Medical)	No. Labs are not state licensed. Department of Health regulates the MMJ program.	Labels must include cannabinoid profile, including THC level.	Not regulated.	Not regulated.

State	State Certification	Testing Requirements	Accreditation/ Lab Requirements	Sampling
DE (Medical)	No. Labs are not state licensed. Department of Health and Social Services regulates MMJ program.	Labels must state: 1. Product is free of contaminants; 2. Active ingredients	No accreditation required. "Compassion centers" must have detailed procedures regarding testing.	"Compassion centers" must have detailed procedures for the selection process and number of samples tested.
IL (Medical)	Yes. Labs must be "approved" by the Dept. Department of Agriculture regulates MMJ program.	Potency required. Label must indicate pass/fail **if** sampled for microbiological, mycotoxins, pesticide, solvent residue	Yes, must be accredited. Labs requirements: 1. Accredited by a private accrediting organization; 2. Independent; 3. Qualified lab director; 4. Certain testing must be measured in colony forming units per gram	Lab employees shall select samples.
MA (Medical)	No. Labs are not state licensed. Department of Public Health regulates MMJ program.	1. Potency; cannabinoid profile; 2. Contaminants including mold, mildew, heavy metals, plant-growth regulators; non-organic pesticides; 3. Additional testing may be required by DOH	Yes, must be accredited. 1. Accredited to ISO 17025 by third party; OR 2. Certified, registered, accredited by an organization approved by DOH Labs must be able to test for the following: 1. THC/CBD potency at a minimum; 2. Lead, mercury, arsenic, cadmium; 3. Pesticide residues and plant-growth regulators 4. Microbiological contaminants; 5. Residual solvents	Representative sampling required from each lot. Detailed sampling guidelines in DOH regulations. Factors to consider when sampling: 1. Homogeneity 2. Physical Form 3. Quantity
MN (Medical)	Yes. Labs must be licensed by the state. Department of Health regulates MMJ program.	1. cannabinoid profile; 2. metals; 3. pesticide residues and plant growth regulators 4. microbiological contaminants and mycotoxins; and 5. residual solvents. Labs must assess: 1. Chemical and microbiological composition; 2. Active ingredients; 3. Shelf life; 4. Presence of inactive ingredients and contaminants	Yes, must be ISO 17025 accredited by 12/31/16. Lab requirements: 1. Operate using proper lab equipment; 2. Must be able to test for content, contamination, metals, pesticide residue and plant growth regulators, microbiological contaminants and mycotoxins, residual solvents, consistency by testing for stability	Random sample from each lot required.

State	State Certification	Testing Requirements	Accreditation/ Lab Requirements	Sampling
NV (Medical)	Yes. Labs must be licensed by the state. Department of Agriculture regulates the MMJ program.	1. Moisture content 2. Potency analysis 3. Terpene analysis 4. Foreign matter inspection 5. Microbial screening 6. Mycotoxin screening 7. Heavy metal screening 8. Pesticide residue analysis	Required quality assurance tests, can be accredited or adopt good lab practices. Random compliance tests. A lab shall: 1. Adopt and follow minimum good lab practices; at a minimum OECD Principles of Good Lab Practice and Compliance Monitoring OR 2. ISO certified Labs requirements: 1. Qualified, scientific director; 2. Follow certain testing methodology - American Herbal Pharmacopoeia; 3. Proficiency testing required	Random, homogenous sample from each lot. Lab must collect samples, unless cultivation facility designates a person responsible for collecting samples in accordance with labs standards. Cultivation facility must file an attestation with the Division describing manner in which samples are selected.
NH (Medical)	No. Labs are not state licensed. Department of Health and Human Services regulates MMJ program.	1. Potency; 2. Residual solvents; 3. Other tests may be requested if contamination is suspected	Yes, must be accredited. 1. ISO 17025; OR 2. ANSI-ASQ National Accreditation Board (ACLASS); OR 3. Clinical Lab Improvement Act (CLIA)	Not regulated.
NM (Medical)	Yes. Labs must be licensed by the state. Department of Health regulates MMJ program.	1. Microbiological; 2. Mycotoxins; 3. Solvent residue; 4. Heavy metals; 5. Potency (CBD/THC) 6. Additional tests may be required. Three Exceptions. Dept may waive testing requirement in whole or in part. 1. Number of labs approved to conduct a given test is insufficient for all testing samples that need to be processed. 2. Dept. may adopt and enforce a standard of staggered implementation. Staggered, random testing of dried usable cannabis and concentrated cannabis products. 3. Exceptions for previously tested lots. If lot was previously sampled and tested by another producer it does not have to be tested.	No accreditation required. Lab requirements: 1. Standard operating procedures; 2. Describe types of testing offered	Samples shall be no more than 3 grams from every lot harvested. 1 gram for concentrates.
NY (Medical)	Yes. Labs must be "approved" by the state. Department of Health regulates the MMJ program.	1. Potency (THC/CBD); 2. Contaminants The registered organization shall demonstrates the stability of each marijuana product (each **brand** and each form).	No accreditation required. Lab requirements: 1. DEA license; 2. Physically located in NY; mobile labs prohibited; 3. Must be approved by the DOH; 4. Describe methods	Subset of each lot. Statistically representative number of samples to allow for testing at least three times. Samples must be retained by organization for at least two years following date of expiration.

State	State Certification	Testing Requirements	Accreditation/ Lab Requirements	Sampling
OR (Medical)	State has its own accreditation for cannabis testing labs. Oregon Environmental Laboratory Accreditation Program (ORELAP). Oregon Health Authority.	1. Potency 2. Pesticides; 3. Mold and mildew; Dispensaries must make sure product is tested before it is sold. Dispensaries may accept test results from growers and/or producers.	Yes, must be accredited. 1. ISO 17025; OR 2. 2009 National Environmental Lab Accreditation Conference Institute TNI Standards Lab requirements: 1. Use valid testing methodology; and 2. Has a quality for testing pesticides, mold and mildew	Random samples from each lot.
WA (Adult use)	Yes. Labs must be state licensed by the Washington State Liquor Control Board.	1. Moisture content; 2. Potency analysis; 3. Foreign matter inspection; 4. Microbiological screening	No accreditation required. Lab requirements: 1. Scientific director; 2. Follow American Herbal Pharmacopoeia testing methodology (or alternative scientifically valid testing method); 3. Board may require third party validation of any monograph or analytical method; 4. Must adopt good lab practice; 5. Must maintain standard operating procedures; 6. Must maintain a quality control program as specified by the Board; Labs can be audited by the Liquor Control Board	Sample sizes are determined based on type of product. Sample is either 2 grams or 1 unit depending on product.

Note: Eight states with regulated medical marijuana programs do not currently require laboratory testing: Arizona, California, Colorado, Maine, New Jersey, Rhode Island, and Vermont. Five states will require laboratory testing but have not yet developed a regulatory system: Hawaii, Maryland, Michigan, Montana, and Washington (Medical).

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